Supplementary appendix

Contents

Web-Appendix 1: MACH-NC collaborative group

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Web-Appendix 2: Inclusion criteria

Trials were eligible if they had accrued previously untreated patients with HNSCC and compared curative loco-regional treatment with loco-regional treatment plus chemotherapy, the addition of another timing of chemotherapy to loco-regional treatment plus chemotherapy (main question), or compared induction chemotherapy and radiotherapy to the same concomitant (or alternating) chemoradiotherapy (secondary question). Chemotherapy and radiotherapy should be similar in both arms. Each trial had to be randomized it would be impossible to know in advance which treatment an individual would receive (avoiding the potential of allocation bias). Trials should be unconfounded, except changes of the radiotherapy in the experimental arm (decreased dose or increased duration without change in fractionation). Trials were eligible if accrual was completed before December 31st 2016, and if all randomized patients had undergone a potentially curative loco-regional treatment and had not been treated for another malignancy. Trials including tumors of the oral cavity, oropharynx, hypopharynx and larynx were included. Trials including only nasopharyngeal carcinomas were excluded.

Web-Appendix 3: Trial search equations

Medline (PubMed)

Search ((laryngeal neoplasms[MeSH Terms] OR mouth neoplasms[MeSH Terms] OR nose neoplasms[MeSH Terms] OR pharyngeal neoplasms[MeSH Terms] OR salivary gland neoplasms[MeSH Terms]) OR (("head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal OR sinus OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn* OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn*) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*))) AND ((squamous OR epidermoid) OR "Carcinoma, Squamous Cell"[Mesh Terms]) AND (drug therapy[MeSH Subheading] OR chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy OR pharmacotherapy OR taxane* OR docetaxel OR paclitaxel OR Taxoid OR taxotere OR cisplatin OR platin* OR carboplatin OR fluorouracil OR 5-fluorouracil OR fluoro-uracil OR 5FU OR hydroxyurea OR tegafur-uracil OR leucovorin OR cetuximab OR bevacizumab OR panitumumab OR tirapazamine OR gefitinib OR erlotinib OR lapatinib OR Nimotuzumab OR gemcitabine OR amifostine OR methotrexate) AND ((randomized controlled trial [pt] OR clinical trial, phase iii [pt] OR clinical trial, phase iv [pt] OR clinicaltrials.gov [si] OR isrctn [si] OR randomized controlled trials as topic [mh]) OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR single-blind OR double-blind) AND (trial OR trials OR study OR studies))) Limits: Publication Date from 2000

SCOPUS

((TITLE-ABS-KEY("head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal) OR TITLE-ABS-KEY(sinus OR pharyngeal OR pharynx OR hypopharyn OR nasopharyn* OR oropharyn* OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn*))) AND ((TITLE-ABS-KEY(chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy OR pharmacotherapy OR taxane* OR docetaxel OR paclitaxel OR taxoid OR taxotere OR cisplatin OR platin* OR carboplatin OR fluorouracil OR 5-fluorouracil) OR TITLE-ABS-KEY(fluoro-uracil OR 5fu OR hydroxyurea OR tegafur-uracil OR leucovorin OR cetuximab OR bevacizumab OR panitumumab OR tirapazamine OR gefitinib OR erlotinib OR lapatinib OR nimotuzumab OR gemcitabine OR amifostine OR methotrexate))) AND ((TITLE-ABS-KEY(random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR single-blind OR double-blind) AND TITLE-ABS-KEY(trial OR trials OR study OR studies))) AND ((TITLE-ABS-KEY(cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*) AND TITLE-ABS-KEY(squamous OR epidermoid))) AND (LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-*

TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000))

Cochrane
"head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal OR sinus OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn* OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn* in Title, Abstract or Keywords and chemotherapy OR "drug therapy" in Title, Abstract or Keywords and squamous in Title, Abstract or Keywords and randomized OR randomised in Title, Abstract or Keywords and cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* in Title, Abstract or Keywords, from 2000 to 2010 in Cochrane Central Register of Controlled Trials

Web of Science (meeting abstract)
Topic=("head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal OR sinus OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn* OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn*) AND Topic=(chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy OR pharmacotherapy) AND Topic=(cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm) AND Topic=(squamous) AND Topic=(random*)
Refined by: Document Type=(MEETING ABSTRACT)
Timespan=2000-2010. Databases=SCI-EXPANDED.

clinicaltrials.gov
random* | Interventional Studies | head and neck cancer AND squamous | drug therapy OR chemotherapy | received on or after 01/01/2000

Web-Appendix 4: Data checking and trial quality

Internal consistency was checked (chronology of dates, extreme values, etc). Randomization validity was assessed by checking patterns of treatment allocation and balance of baseline characteristics between treatment groups. Post-randomization exclusion were systematically searched. Follow-up of patients was also compared between treatment groups. All data were compared to trial protocols and published reports. All questions raised by the checking procedure were discussed with the trialists [1].

We were able to collect data from 725 of the 867 randomized patients who had been excluded from the original published analyzes. For 89 trials out of 107, data were available for all randomized patients. Numbers of analyzed and randomized patients are available for each trial in Web-Tables 1, 2, 3, and 4. No significant difference due to randomization was observed between treatment arms, except for two trials in which follow-up was significantly different [2–4]*. In agreement with the investigators, follow-up was censored for these two trials. None of the trials identified for this update were excluded because of randomization or follow-up problem. Trials previously excluded after checking the individual patient data are available in the publications of the initial meta-analysis and its first update [5,6]. Because of the difficulty to detect quality problem in small trials, a sensitivity analysis without small trials was performed (Web-Table 10).

** Hitt R, Grau J, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Annals of Oncology 2014;25:216–25. https://doi.org/10.1093/annonc/mdt461. (update reference 2)*

Web-Appendix 5: Statistical methods

Power of the analysis

With more than 18000 patients (and at least 12000 deaths), an absolute improvement in survival from 30% to 33% at 5 years could be detected with a power of 99.9% (two-sided log-rank test, α=5%). For the population included in the 4 main analyzes on OS (3 analyzes by timing for the main question and the secondary question) that ranged from 1214 to 10680 patients, this power ranged 22% from to 94% to detect a 3% difference from 30% to 33%. For the analysis with 1214 patients, the power was 82% to detect a 7.5% difference from 30% to 37.5%.

120-day mortality

Hazard ratio and Peto curves were estimated with Peto method (O-E and Var(O-E)). Patients with a follow-up longer than 120 days were censored at 120 days.

Heterogeneity
In case of significant heterogeneity ($p<0.10$), analysis was repeated without the "outliers" defined as trials with a 95% CI that did not overlap the 95% CI of the global HR). If heterogeneity was still significant, a random-effects model was used [7]. We computed residual heterogeneity within trial subgroups by subtracting the Chi^2 statistic of the heterogeneity test between groups from the Chi^2 statistic of the overall heterogeneity test [8].

Cancer/non-cancer mortality, survival within and after 5 years
Expected (E) and observed (O) numbers of events were derived from the log-rank statistic (method developed by R Peto)[9]. Cancer mortality was obtained indirectly by subtracting (O-E) and its variance (Var(O-E)) of non-cancer mortality from (O-E) and Var(O-E) of overall survival [10]. Cancer/non-cancer mortality was studied only for the induction and concomitant timings, and was restricted to recent and more homogenous trials: for induction comparisons, only trials using PF or TPF schedules; for concomitant comparison, only trials included in the updates. Moreover, only trials with data on tumour failures and cause of death were included.
Overall survival after 5 (10) years was obtained indirectly by subtracting (O-E) and Var(O-E) of overall survival within 5 (10) years from (O-E) and Var(O-E) of overall survival on the whole period of time [10].

Competing risk

Only the first type of failure (loco-regional or distant) were collected. Fine and Gray model stratified on trial comparisons was used with three types of event: loco-regional failure, distant failure, and death without failure [11]. Each type of event was successively analyzed as the main event. The others were considered as competing events. Patients alive without failure were censored at the date of last follow-up. Results of the "death without failure" analysis are not presented in this publication but are available on request. Cumulative incidence curves were drawn according to the Aalen Johanssen method and were not stratified.

Analyzes were performed with R software (version 3.3.2, R foundation for Statistical Computing, Vienna, Austria). Sub-distribution HR were estimated in each trial with the "cmprsk" package and global sub-distribution HR were estimated with the "crrSC" package.

Sensitivity, subset and subgroup analyzes

Sensitivity, subset and subgroup analyzes were pre-specified in the protocol except if mentioned otherwise in this publication.

Six sensitivity analyzes (i.e. analysis after exclusion of some comparisons) were performed for each timing: a) without comparisons with two timing (e.g. concomitant radio-chemotherapy vs. induction chemotherapy plus concomitant radio-chemotherapy); b) without confounded comparisons; c) without trials starting accrual before 1980; d) without trial including 80 patients or less or 40 patients or less by arm; e) without trials with a median follow-up of 5 years or less; d) after exclusion of duplicated patients. For the induction timing, because of the apparent contradiction between the previous meta-analysis comparing PF and TPF induction chemotherapy [12] and the current results, unplanned analyzes were performed after exclusion of the 3 comparisons with major early related to treatment mortality and/or without GCSF (Budapest 2007, TTCC 2002 PF and TPF without GCSF) [12,13].

Subgroup analyzes (i.e. interaction between patient characteristics and treatment effect) were performed only for the induction and concomitant timings, and were restricted to recent and more homogeneous trials: for induction comparisons, only trials using PF and TPF schedules; for concomitant comparisons, only trials included in the updates. Only trials with all categories of the studied characteristic were included. For instance, if age is analyzed in four categories (<50, 50-59, 60-69, ≥ 70), trials without patients 70 or older were excluded. Between trials heterogeneity was studied using the Fisher et al method [14]. As in MARCH, subgroup analyzes with adjustment on covariables available for most of the patient (age, sex) were performed as sensitivity (unplanned) analyzes. In the absence of recent trial, no subgroup analysis was performed for the adjuvant comparisons and the secondary question (see text below Web-Table 12-B).

Web-Appendix 6: Results of trials search

Following trial search, 16 new trials were identified as potentially eligible for this meta-analysis. Four of those trials were excluded: a three-arm trial was considered too small (N=60)[15], one investigator reported his trial as not suitable enough for publication (N=275)[16], data of one trial were lost (N=105)[17], one trial was excluded after data collection because it compared two larynx preservation approaches (N=75)[18].

Data of three trials were collected at the time of the initial meta-analysis but were not included back then because they studied the addition of a second timing of chemotherapy to another timing plus loco-regional treatment. They were included in this second update (N=210)[19–21].

One trial, INRC-HN-9 [22] included in the first update was transferred to the MARCH meta-analysis (N=143)[23]. One trial, TMH 1114 identified for the MARCH meta-analysis was also eligible for MACH-NC (N=131)[24].

Trials not available or excluded in the initial meta-analysis or in the first update are described in the corresponding publications [5,6].

Among the 107 trials included in the second update of the meta-analysis, five were unpublished: BNH 003 (N=124), EORTC 24844 (N=139), EORTC 22954 (N=59), EORTC 22962 (N=54), SECOG II (N=239).

Web-Appendix 7: Trial design, trial division and patient duplication

Trial design

Three trials were analyzed as several independent randomized trials since the initial meta-analysis. Among those three trials, two were divided into two independent randomized trials based on their loco-regional treatments: GETTEC neo1 and GETTEC neo2 [25], HNU-87a and HNU-87b [26]. The third trial was analyzed as three independent randomized trials because the route of drug administration differed: WIA-OC5a, WIA-OC5b and WIA-OC5c [27].

Out of the 107 randomized trials included in the second update of the meta-analysis, 15 were three-arm trials (SECOG II unpublished)[2,24,28–40]. They were analyzed as follows:

- Third arm was not eligible in six trials: TMH 1114, Barcelona, Vienna, RTOG 9111, Oro 9301, Pité 74 [24,28–33];

- The two experimental arms were pooled in three trials: Buenos Aires, Kragejuvac 1, HeCOG 9405 [34–36].

The three arms were taken into account for the six other trials: Lucknow 95, TTCC 2002, HNCP, AC Camargo, Int 126, SECOG II (unpublished) [2,37–40].

Design was a 2x2 factorial plan in six trials. In three of those trials, factorial plan applied only on a part of the population (SECOG II unpublished; GSTTC 2501 [41,80], UKHAN [42]); in one trial, a second randomization was performed (+/- G-CSF; Cologne 95)[43]; in two trials, a second randomization was performed (+/- radiotherapy) (EORTC 22962 unpublished, Pitié 81)[44]. Second randomization was not taken into account for two trials (Cologne 95, Pitié 81) and led to the exclusion of a part of the trial in GSTTC 2501 trial in which the second randomization was between cetuximab and cisplatin [41,80].
There was an imbalanced randomization in five trials: SECOG II (unpublished), TTCC 2002, MDA-70, UKHAN, IAR-92 [2,42,45,46].

Trial division

To study treatment effect according to chemotherapy timing, loco-regional treatment and type of chemotherapy drug, some trials were divided into several comparisons because of their designs. In some cases, it led to patient duplication. Details of these divisions are available in Web-Table 5.

Patient duplication

According to the analysis performed, duplicated patients were:

1/ Main question (addition of chemotherapy, 130 comparisons): 8.2% (1698/20649)
- Induction chemotherapy (45 comparisons): 4.7% (330/7054)
- Concomitant chemotherapy (71 comparisons): 1.3% (144/10680)
- Adjuvant chemotherapy (14 comparisons): 0% (0/2915)

2/ Secondary question (direct comparison of induction and concomitant chemotherapies, 8 comparisons): 0% (0/1214).

Re-analysis with correction for duplication [47], led to similar results (data not shown).

Web-Appendix 8: Heterogeneity between comparisons and sensitivity analyzes

Induction comparisons

No significant heterogeneity was observed, except for loco-regional ($p<0.0001$; $I^2=63\%$) and distant failure ($p<0.0001$; $I^2=97\%$). After the exclusion of outliers (3 comparisons for LRF and 7 for DF), heterogeneity became non-significant. The sub-hazard ratio was 0.99 ([0.91; 1.08], p=0.88) for LRF and similar for DF (data not shown).

Concomitant comparisons

Significant heterogeneity was observed both for overall (p=0.0002; 42%) and event-free survival ($p<0.01$; 30%). In both cases, the heterogeneity was observed only among the comparison of the initial meta-analysis which have been explored previously [48] and the hazard ratios were not significantly different between the initial meta-analysis and the updates (Web-Figure 10 for OS; data not shown for EFS).

For 120-day mortality, the heterogeneity observed (p=0.01, $I^2=30\%$; Web-Figure 5) was not significant anymore after exclusion of six outliers (p=0.45, $I^2=1\%$): UW-77 [49], UW-79 [50], CH-7401 [51], ORO 9301 [28], UKHAN1po1 [42] and Lucknow 90 [52] (5% of Var(O-E) for this timing). Without those outliers, HR was 1.12 [0.96; 1.31].

A significant heterogeneity was observed for loco-regional ($p<0.0001$; $I^2=85\%$) and for distant failure ($p<0.0001$; $I^2=96\%$). After the exclusion of outliers (5 comparisons for LRF and 6 for DF), heterogeneity became non-significant with similar results in both cases (date not shown).

Adjuvant comparison

For event-free survival, a significant heterogeneity was observed (p=0.03, 47%; Figure 1). After the exclusion of the outlier (one comparison), heterogeneity became not significant with similar results (data not shown).

For 120-day mortality, a borderline heterogeneity was observed (p=0.10, $I^2=34\%$). After the exclusion of UKHAN1a1 [42] (9% of Var(O-E) for this timing), heterogeneity became non-significant (p=0.48, $I^2=0\%$) but the deleterious effect was still significant (HR=1.61 [1.12; 2.33]).

A significant heterogeneity was observed for distant failure ($p<0.0001$; $I^2=98\%$). After the exclusion of outliers (4 comparisons), heterogeneity became non-significant. Sub-hazard ratio was equal to 0.81 [0.65; 1.02], p=0.07.

Secondary question

For the secondary question (concomitant [or alternating] radio-chemotherapy versus induction [+/- adjuvant] chemotherapy and radiotherapy), no significant heterogeneity was observed (Web-Figure 12).

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Web-Table 1: Description of induction trials

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized[µ]	Median follow-up [95% CI] (years)
Chemotherapy other than platin + fluorouracil or Taxane + platin + fluorouracil									
IGR-65[53]	1965–67	OC, OP	IV	Mx (ia) LA (im)	50 mg x 6–12 15 mg x 6–12	RT	30-60 Gy	36/39[a]	NA[†]
RTOG 6801[54]	1968–73	OC, OP, HP, L	III, IV	Mx	25 mg x 5	RT	55-80/5-10 wks	680/712[b]	4.3 [4.0 ; 4.8]
EORTC 24771[55]	1977–82	HP	II to IV	B Mx Vc	15 mg 20 mg/m^2 x 4 1.5 mg/m^2	S + RT	50-65 Gy /≤10 wks	231/231[c]	5.9 [4.9 ; 6.6]
Denver 77[56]	1977–83	OC, OP, HP, O	III, IV	B C Mx	10 U/m^2 x 4, wks$_{1,4 \text{ or } 5}$ 50 mg/m^2, wks$_{1,4 \text{ or } 5}$ 30 mg/m^2 x 2, wks$_{1,4 \text{ or } 5}$	RT or S + RT	60-70 Gy, alt 50-60 Gy, alt	59/59[d]	NA[†]
HNCP[38]	1978–82	OC, HP, L	II to IV	Arm$_1$: B (bolus) B (ci) C Arm$_2$: Arm$_1$ + C	ind: 15 mg/m² d$_3$ ind: 15 mg/m² d$_{3\text{-}7}$ ind: 100 mg/m² d$_1$ adj : 80 mg/m² monthly x 6	S + RT	50 Gy/5-5.5wks	462/462[e]	5.3 [5.1 ; 5.5]
EORTC 78-OCP[57]	1978–84	OC, OP	I to IV	B (ia) Vc (ia)	15 mg d$_{1\text{-}12}$ 1 mg, d$_{1,5,9}$	S or S + RT	NA MD	225/225[f]	4.9 [4.5 ; 5.3]
MCW-1[58,59]	1979–82	OC, OP, HP, L, NP, O	III, IV	B Cy F Mx	30 U x 4, wks$_{1,4}$ 200 mg/m² x 5, wks$_{1,4}$ 400 mg/m² x 5, wks$_{1,4}$ 30 mg/m² x 5, wks$_{1,4}$	RT or RT + S	70 Gy/7wks 50 Gy/5wks	83/83[g]	5.9 [3.3 ; 17.1]
SWOG 8006[60]	1980–85	OC, OP, HP, L	II to IV	B C Mx Vc	15 U/m² d$_{1,8}$, wks$_{1,4,7}$ 50 mg/m², wks$_{1,4,7}$ 40 mg/m², wks$_{1,4,7}$ 2 mg, wks$_{1,4,7}$	S + RT	MD	167/167	13.7 [11.6 ; 14.5]
Pitié-81[44]	1981–85	OC, OP, O	I to IV	A B (im) C Vc	60 mg, 3 cycles 15 mg x 3 150 mg 2 mg	RT	70 Gy/7 wks or 60 Gy/4 wks, sc, bf	112/116[h]	11.3 [4.4 ; 12.9]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized[μ]	Median follow-up [95% CI] (years)
Buenos Aires[34]	1981–86	OC, OP, HP, L, NP	III, IV	$\underline{Arm_1}$: C B $\underline{Arm_2}$: C B Mx	100 mg/m², $d_{1,15}$ 40 mg/m², $d_{1,8,15,22}$ 100 mg/m², $d_{4,19}$ 40 mg/m², $d_{1,8,15,22}$ 50 mg/m², $d_{1,15}$	S	NA	120/120[i]	7.0 [6.1 ; 8.9]
						or RT	MD		
						or S + RT	MD		
Créteil-82[61]	1982–87	OC, OP	II to IV	B (ci) F Mx LA (po) C	10 mg/m² x 5, $wks_{1,5,9}$ 600 mg/m² d_2, $wks_{1,5,9}$ 120 mg/m² d_2, $wks_{1,5,9}$ 10 mg x 4, d_3, $wks_{1,5,9}$ 120 mg/m² d_4, $wks_{1,5,9}$	RT	70 Gy/7.8 wks	122/131[j]	5.0 [4.2 ; 5.7]
						or S + RT	55 Gy/6 wks		
HNCGIC 02[62]	1983–86	OC, OP, HP, L	II to IV	B (ci) C Mi Vd	12.5 mg/m² x 4, $wks_{1,4}$ 20 mg/m² x 4, $wks_{1,4}$ 10 mg/m², $wks_{1,4}$ 2.5 mg/m², $wks_{1,4}$	RT	65-75 Gy	100/100[k]	10.2 [9.8 ; 12.3]
AC Camargo[39]	1984–86	OC, OP, HP	III, IV	B C Mi Vb	10 mg/m², $wks_{1 \pm 2}$ 30 mg/m² x 2, $wks_{1 \pm 2}$ 8 mg/m², $wks_{1 \pm 2}$ 4 mg/m², $wks_{1 \pm 2}$	RT	70 Gy/7 wks (Co) or 8 wks (Ex)	60/60[l] ¶	6.5 [3.6 ;]*
SECOG II (unpublished)	1984–89	OC, OP, HP, L, NP, O	III, IV	B (im) Mx LA (iv) LA (im) Vc Or the same + F	30 mg, $wks_{1,3,13,15}$ 200 mg, $wks_{1,3,13,15}$ 50 mg, $wks_{1,3,13,15}$ 15 mg x 6, $wks_{1,3,13,15}$ 1.5-2 mg, $wks_{1,3,13,15}$ 500 mg, $wks_{1,4,6,9}$	RT	60-66 Gy/6.5 wks	163/163[m]	12.5 [12.1 ; 15.0]
HNCGIC 03[63]	1986–89	OC, OP, HP, L	II to IV	C (ci) F (ci) Vd	40 mg/m² x 3, $wks_{1,4,7}$ 600 mg/m² x 5, $wks_{1,4,7}$ 3 mg/m² x 2, $wks_{1,4,7}$	RT	70 Gy	108/108[n]	7.2 [6.7 ; 7.5]
Songkhla [64]	1988–92	OC, OP, HP, O	III, IV	B (ci) C Mx	10 mg/m² d_{3-7}, $wks_{1,5}$ 20 mg/m² x 5, $wks_{1,5}$ 40 mg/m² $d_{15,22}$, $wks_{1,5}$	S + RT	≥ 60 Gy	54/54[o]	4.1 [2.8 ; 5.3]
Lucknow 95[37]	1995–99	OC, OP, HP, L, O	III, IV	C	35 mg/m² d_1, wks_{1-7}	RT	70 Gy/7 wks	200/200[p,$]	13.0 [10.4 ; 14.5]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized[u]	Median follow-up [95% CI] (years)
Platin + fluorouracil only									
MCW-2[65,66]	1983–86	OC, OP, HP, L, NP, O	III, IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 500 mg/m^2 x 5, wks$_{1,4,7}$	RT + S or RT	50 Gy/5 wks 70 Gy/7 wks	63/63[q]	8.3 [5.6 ; 11.0]
EORTC 24844 (unpublished)	1985–91	OP	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	S + RT	50 Gy/5 wks +/- 15 Gy boost	139/139[r]	2.8 [2.2 ; 3.8]
SHNG-85[67]	1985–92	OC, OP, HP, L	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	RT	64-70 Gy/6.5-7 wks	461/461[s]	7.2 [6.9 ; 7.5]
Créteil-86[68,69]	1986–89	OC, OP, HP, L	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	RT or S + RT	70 Gy/8 wks 55 Gy/6 wks	156/156[t]	6.0 [5.3 ; 6.0]
GSTTC-86[70,71]	1986–90	OC, OP, HP, O	III, IV	C F (ci)	100 mg/m^2, wks$_{1,4,7,10}$ 1000 mg/m^2 x 5, wks$_{1,4,7,10}$	RT or S + RT	65-70 Gy/6.5-7wks 45-50 Gy/4.5-5wks	237/237[u]	11.3 [10.2 ; 11.6]
GETTECneo1[25]	1986–91	OP	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	RT	70-75 Gy/7-7.5 wks	174/174[v]	12.0 [11.0 ; 12.8]
GETTECneo2[25]	1986–92	OP	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	S + RT	50-65Gy/5-6.5 wks	144/144[w]	12.3 [11.1 ; 12.8]
AHNTG[72]	1986–93	OC, OP, HP, L, NP, O	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 4, wks$_{1,4,7}$	S or RT or S + RT	NA MD MD	280/280[x]	7.1 [6.7 ; 7.7]
Las Palmas[73]	1987–89	OC, OP, HP, L, NP	III, IV	Cb Tg (po)	400 mg/m^2 , wks$_{1,5,9}$ 1000 mg/m^2 x 14, wks$_{1,5,9}$	RT	66-74 Gy/6.5-7.5 wks	36/42[y]	3.2 [2.6 ; 4.0]
Rennes-87[74]	1987–90	OP, HP	I to IV	C F (ci)	100 mg/m^2, wks$_{1,3,5}$ 1000 mg/m^2 J$_{2\text{-}5}$, wks$_{1,3,5}$	RT or S + RT	68.6 Gy MD	133/133[z]	6.4 [5.5 ; 7.4]
Parma[75]	1987–91	OC, OP, HP, L	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7 \pm 10,13}$ 1000 mg/m^2 x 5, wks$_{1,4,7 \pm 10,13}$	S or RT or S + RT	NA MD MD	69/69[aa]	6.2 [5.6 ; 6.8]
CFHNS[76,77]	1988–91	OC, OP, HP, L	II to IV	Cb F (ci)	400 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	RT or S + RT	75 Gy 45-75 Gy	324/324[bb]	5.7 [5.3 ; 6.0]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized[μ]	Median follow-up [95% CI] (years)
Cologne 88[78]	1988–93	OC, OP, HP	II to IV	Cb F (ci)	360 mg/m^2, wks$_{1 \pm 5 \pm 9}$ 1000 mg/m^2 x 5, wks$_{1 \pm 5 \pm 9}$	S + RT	60-66 Gy/6-7 wks	97/97[cc]	2.0 [1.6 ; 2.5]
HNAP-02[79]	1989–92	OC, OP, HP, L	III, IV	C F	70 mg/m^2, 2 cycles 660 mg/m^2 d$_{2\text{-}6}$, 2 cycles	S or S + RT	50 Gy 50 Gy	50/50[dd]	5.2 [4.1 ; 5.6]
BNH 003 (unpublished)	1990–92	OC, OP, HP, O	III, IV	C F	100 mg/m^2 x 2–3 4000 mg/m^2 x 2–3	S + RT	45-60 Gy	124/124	3.7 [3.4 ; 4.0]
Taxane + platin + fluorouracil (second update) [$]									
TTCC 2002[2]	2002–07	OC, OP, HP, L	III, IV	Arm$_2$: Do C F (ci) Arm$_3$: C F (ci) C (3 arms)	 ind: 75 mg/m², wks$_{1,4,7}$ ind: 75 mg/m², wks$_{1,4,7}$ ind: 750 mg/m² x 5, wks$_{1,4,7}$ ind: 100 mg/m², wks$_{1,4,7}$ ind: 1000 mg/m² x 5, wks$_{1,4,7}$ conco: 100 mg/m², wks$_{1,4,7}$ of RT	RT	70 Gy/7 wk	387/387[ee]	5.0 [5.0 ; 5.0]
GSTTC 2501[41,80]	2003–12	OC, OP, HP, O	III, IV	C Do F (ci) C (ci; 2 arms) F (ci; arms)	ind: 80 mg/m², wks$_{1,4,7}$ ind: 75 mg/m², wks$_{1,4,7}$ ind: 800 mg/m² x 4, wks$_{1,4,7}$ conco: 20 mg/m² x 4, wks$_{1,6*}$ conco: 800 mg/m² x 4, wks$_{1,6*}$ *of RT	RT	70 Gy/7 wks	261/261[ff]	3.7 [3.4 ; 3.9]
DeCIDE[81]	2004–09	OC, OP, L, NP, O, U	IV	Do C F (ci) Do (2 arms) F (ci, 2 arms) Conco in 2 arms Hu (po) Hu (po)	ind: 75 mg/m², wks$_{1,4}$ ind: 75 mg/m², wks$_{1,4}$ ind: 750 mg/m² x 5, wks$_{1,4}$ conco: 25 mg/m², wks$_{1,3,5,7,9*}$ conco: 600 mg/m² x 5, wks$_{1,3,5,7,9*}$ conco: 500 mg x 2, d$_{1\text{-}5}$, wks$_{1,3,5,7,9*}$ conco: 500 mg, d$_6$, wks$_{1,3,5,7,9*}$ * of RT	RT	75 Gy/9 wks, bid, sc	285/285[gg]	6.0 [5.6 ; 6.4]
Budapest 2007[13]	2007–09	OC, OP, HP, L	III, IV	Do C F (ci) C (two arms)	ind: 75 mg/m²,wks$_{1,4}$ ind: 75 mg/m², wks$_{1,4}$ ind : 750 mg/m² x 4, wks$_{1,4}$ conco: 100 mg/m², wks$_{1,4,7}$ of RT	RT	70 Gy/7 wks	66/66[hh]	6.8 [6.1 ; 7.6]
Shanghai 2008 [82,83]	2008–10	OC	III, IVa	Do C F (ci)	75 mg/m², wks$_{1,4}$ 75 mg/m², wks$_{1,4}$ 750 mg/m² x 5, wks$_{1,4}$	S + RT	54-60 Gy/6 wks	256/256[ii]	5.6 [5.4 ; 5.8]

* Upper value not reached. [†] Median follow-up and 95% confidence interval not available for two trials because of high rate of mortality. [μ] Number of patients analyzed in the meta-analysis and corresponding number of patient randomized. [$] Trial not included in initial MACH-NC or its first update.

A: Doxorubicin ; AC Camargo: Hospital AC Camargo ; Adj: Adjuvant ; AHNTG: Australian Head and neck Trial Group ; B: Bleomycin ; BNH: B. Nanavati Hospital ; C: Cisplatin ; Cb: Carboplatin ; CFHNS: Carboplatin French Head and Neck Study ; ci: Continuous Infusion ; conco: Concomitant ; Co: Control arm ; DeCIDE: Docetaxel-based Chemotherapy plus or minus Induction chemotherapy to Decrease Events ; Do: Docetaxel ; EORTC: European Organisation for Research and Treatment of Cancer ; Ex: Experimental arm ; F: 5-Fluorouracil ; GETTEC: Groupe d'Etude des Tumeurs de la Tête Et du Cou ; GSTTC: Gruppo di Studio sui Tumori della Testa et del Collo ; Gy: Gray ; HNAP: Head and Neck Adjuvant Project ; HNCGIC: Head and Neck Cancer Group of Institut Curie ; HNCP: Head and Neck Contract Program ; HP: Hypophraynx ; Hu: Hydroxyurea ; ia: intrarterial ; IGR: Institut Gustave Roussy ; im: intramuscular ; ind: Induction ; iv: intravenous; L: Larynx ; LA: Leucovorin ; MCW: Medical College of Wisconsin ; MD: Missing Data ; Mi: Mitomycin ; Mx: Methotrexate ; NA: Not Applicable ; NP: Nasopharynx ; NR: not reached; O : Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per os ; RT: Radiotherapy ; RTOG: Radiation Therapy Oncology Group ; S: Surgery ; SECOG: South of England Co-operative Oncology Group ; SHNG: Scandinavian Head and Neck Group ; SWOG: SouthWest Oncology Group ; Tg: Tegafur ; TTCC: Tratamiento de Tumores de Cabeza y Cuello ; U : Unknown primary ; Vd: Vindesine ; Vc: Vincristine ; wks: weeks

[a] Radiotherapy started 2 weeks after the end of ia infusion. 30 Gy was administered over 2 week period. Radiotherapy was stopped if progression was observed; it could be continued up to 60 Gy or followed by curietherapy or even surgery. 16 pts (8 in each arm) received at least 50 Gy.
[b] Mx every third day for 5 injections. Surgical intervention (either resection of the primary or radical neck dissection) was permitted after radiotherapy provided that the some policy was carried out in both arms. Surgery was also permitted as part of an integrated combined treatment regimen.
[c] Only one cycle of chemotherapy, postoperative radiotherapy within the 3 months, 50 Gy plus 15 Gy in limited area in case of unclear tumour margins, not to exceed 10 weeks.
[d] For the operable patients of the control arm, radiotherapy dose was 50 Gy followed by surgery if patient seemed resectable, patients who remained inoperable or refused surgery received another 15-20 Gy. In the experimental arm, after the first cycle of CT on week 2-3, patients received 20 Gy in 10 fractions, a second cycle on wks 4/5, and if resectable, surgery on wks 6-7 plus 40 Gy in 20 fractions when healing seemed complete; those who remained inoperable received another 40-50 Gy. At randomization, 31 were considered as inoperable and 28 as operable.
[e] Three-arm trial with one induction and one induction plus adjuvant.
[f] In the floor of mouth group, postoperative radiotherapy was delivered depending upon the lymph node involvement and the completeness of tumor resection. In this group, tumor bed was irradiated in 68% in chemotherapy arm and 55% in control arm. Irradiation was systematically applied in the posterior oral cavity or oropharynx group.
[g] 2 Gy/fraction. Irradiation was initiated 3 weeks after the last cycle of chemotherapy. Radiotherapy alone was delivered for 46 patients and preoperative radiotherapy plus surgery 36 patients. One additional patient expired in the experimental arm prior the planned irradiation. Initially, responders to induction chemotherapy were scheduled to receive two post-operative cycles of B-CMF using 50% of the induction bleomycin dose. Toxicities and poor compliance with postoperative B-CMF led to discontinue postoperative chemotherapy, testing only induction chemotherapy as outlined.
[h] 3 cycles of chemotherapy planned. Duration of cycle, 3 or 4 weeks? There was a second randomization between standard radiotherapy and bi or tri-fractionated radiotherapies. Standard radiotherapy: 2 Gy/ fraction, 5 fractions a week on 7 wks. Bi-fractionated RT: 1.5 Gy x 2 (4 hours between sessions) , 10 sessions in 5 days, 2 weeks break, similar one week session.
[i] Three-arm trial with 2 chemotherapy arms (A1, A2), BC, BCMx, two 2-wks cycles.
[j] Radiotherapy only (51 patients out of 116 eligible patients), 70 Gy, 1.8 Gy/fraction, 5 fraction by week ; Surgery + radiotherapy (65 patients out of 116 patients), 55 Gy in 6 wks, boost to 70 Gy if incomplete resection. Locoregional treatment decided before randomization.
[k] Two cycles of chemotherapy. Tumor response was evaluated after 50-55 Gy. Surgical excision was performed if the response was < 50% (6 pts). Otherwise the radiotherapy was completed to 65-75 Gy in 1.8 -2.2 Gy per fraction. Mean tumor dose was 69 and 70.3 Gy in the chemotherapy + radiotherapy and radiotherapy arm respectively with mean overall duration of 49 and 49.7 days and mean number of fraction of 34.8 and 34.5 respectively.

[l] ¶Three-arm trial with a concomitant arm and 90 patients overall. Same total dose was delivered in both arms: 2 Gy/fraction over 7 weeks in control arm; 1.8 Gy/fraction over 8 weeks in the experimental arm. Second cycle was given 3 weeks later to the patients in partial response. Patients stable or progressing started radiotherapy immediately. In this group 6 patients did not start RT.

[m] Three-arm trial with a concomitant arm and 239 patients overall; patients allocated to the chemotherapy arms were randomized to receive B/Mx/Vb or same chemotherapy plus F. Two cycles of chemotherapy before radiotherapy and two after. Radiotherapy starting on weeks 5.

[n] Three cycles of chemotherapy. Tumor response was evaluated after 55 Gy. Surgical excision was performed if the response was < 50% (10 patients). Otherwise the radiotherapy was completed to 70 Gy. Mean tumor dose was 68 and 66.6 Gy in the chemotherapy + radiotherapy and radiotherapy arm respectively with mean overall duration of 47.4 and 47.7 days and mean number of fraction of 33 Gy in both arms.

[o] Radiotherapy started within 6 weeks, minimum 60 Gy.

[p] Three-arm trial with 300 patients overall: radiotherapy, induction chemotherapy and radiotherapy, radiotherapy and concomitant chemotherapy. Same chemotherapy in both experimental arms.

[q] 2 Gy per fraction; 70 Gy in favorable tumor site: 7 patients in chemotherapy group and 5 in control;

[r] Surgery + radiotherapy in case of progression after first cycle of chemotherapy or progression or stable disease after the second cycle. Radiotherapy started as soon as possible after complete wound healing. If delayed for more than 10 days, radiotherapy is not mandatory anymore. Dose of 50 Gy in 25 fractions, 5 times a week plus 14 Gy in 7 fractions if the excision was irradical.

[s] 2 Gy by fraction, 5 times a weeks.

[t] Operable patient: 55 Gy over 6 weeks, 1.8 Gy per fraction, 5 days a week, boosted to 70 Gy is residual disease; Inoperable patients: 70 Gy over 8 wks in 1.8 Gy per fraction. Non responding patients were switched to definitive local treatment after 1-2 cycles. Locoregional treatment was decided before randomization.

[u] For operable patients (n=66), 45-50 Gy of adjuvant radiotherapy was planned. Modality of surgery was decided before randomization: 5 patients had no surgery of incomplete surgery. For the inoperable patients (n=171), the planned dose was 65-70 Gy with 2 Gy per fraction and 5 fractions per week. A two-week break was allowed after 40 Gy or in case of grade 3-4 mucositis. Patient level information on planned locoregional treatment was available and the trial was split in two strata: GSTCC 86 and GSTTC 86po (n=66), po for post-operative radiotherapy.

[v] Radiotherapy began 2-3 wks after chemotherapy completion: 70 Gy in 7 weeks with 5 Gy added in case of residual disease

[w] Radiotherapy began within 10 weeks after surgery that was performed 2-3 after chemotherapy completion: 50 Gy in 5 weeks with 2 Gy fraction in patients with free surgical marginal and 65 Gy in 6.5 weeks in case of positive margins.

[x] 36/280 (24%) patients were treated by surgery, 113/280 (76%) patients were treated by surgery and radiotherapy, 118/280 patients by radiotherapy alone, 10 patients had no locoregional treatment, one mixed locoregional treatment and for 2 patients, locoregional treatment was unknown. Protocol mentioned “Radiotherapy should be given in radical doses. In general, fields for DLT (radiotherapy and surgery) should be based upon the original tumour extent, not on its extent following chemotherapy”.

[y] 2 Gy by day, 5 days a week. Surgery was performed after radiotherapy, if disease persisted or recurred (9 patients). Tg daily 1000 mg/m² dose was fractioned into two

[z] 28 patients had surgery plus postoperative and 90 only radiotherapy. Mean dose of radiotherapy was 68.6 Gy+/-6 without difference between the two arms. For the 15 other patients, 5 were ineligible (associated diseases), 4 had protocol violation (chemotherapy dose), 3 refused treatment and for 3 died during chemotherapy.

[aa] Patients achieving complete or partial responses > 80% received two further cycles.

[bb] For radiotherapy alone, a dose of 75 Gy was used. For basilingual and T2 tonsillar tumors a dose of 45-50 Gy was used followed by brachytherapy 30-35 Gy. Post-operative dose ranged from 45 to 75 Gy depending of the degree of resection. Patients showing complete tumor regression switched to radiotherapy alone. Out of the 34 patients in complete response, 29 switched to radiotherapy alone, the other being planned to receive radiotherapy alone. Of the 143 evaluable patients who underwent chemotherapy, 37 out of 90 with primary indication of locoregional surgery qualified for treatment modification, including 21 out of 73 with primary indication of mutilating surgery. Confounded trial (see definition in WEB-Table 3.

[cc] Patients without response after the first cycle were operated immediately. Only patient with patient response after two cycles received the third one. Radiotherapy started at least 6 weeks after surgery. In case of insufficient wound healing at 6 weeks, no RT was performed. Daily fraction was 2 Gy, with 5 fractions a week.

[dd] When nodes metastases were found to be multiple or extracapsular, or surgical margin were insufficient, radiotherapy of 50 Gy was administered post-operatively

[ee] Three-arm trial: CF, DoPF, no induction, with concomitant cisplatin in the three arms and 439 patients overall. Dose of C and F were higher in the CF arm than in the DoCF arm. G-CSF administration from the first cycle to patients assigned to TPF, was implemented in the protocol, by amendment, to prevent neutropenia, after the inclusion of 338 patients. Once the planned 128 patients at the CCRT-alone arm were recruited, the last 52 patients were only randomly assigned to DoCF -CCRT and PF-CCRT arms. Significant unbalance between arms on the median of follow-up was observed, mostly due to difference in the follow-up after 5 years. For this meta-analysis, the last 52 patients were excluded and the follow-up censored to 5 years.

[ff] Two by two design: addition of induction DoCF to radiotherapy plus concomitant treatment; radiotherapy + cisplatin vs radiotherapy + cetuximab. The two cetuximab arms were not eligible for this meta-analysis. Then, only 261 patients out of 421 were included. The trial was a phase II/III that started by the randomized phase II (XRP 6976) comparing induction DoCF to radiotherapy + concomitant cisplatin vs. radiotherapy + concomitant cisplatin. Antibiotic prophylaxis was administrated after each TPF cycle.

[gg] Radiotherapy: 1.5 Gy/fraction, bid, 5 days per week, 5 two-week cycles (one week on/one week off). White blood cell growth factor support was administered with each cycle of IC. Three-dimensional conformal radiotherapy or intensity-modulated radiation therapy were used.

[hh] Phase 2 on the addition of induction CT to concomitant radio-chemotherapy with sample size of 92 and tumor response after radiotherapy as main endpoint. Recruitment was stopped prematurely because of 3 deaths due to febrile neutropenia in the experimental arm. Radiotherapy schedule was 2 Gy per day, 5 days per week. Granulocyte colony-stimulating factor (G-CSF) was administered in febrile and grade 4 neutropenia.

[ii] 1.8-2 Gy/fraction, 5 days a week

Web-Table 2: Description of concomitant trials

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized [µ]	Median follow-up [95% CI] (years)
Initial meta-analysis									
MDA-70[45]	1970–72	OC, OP, HP, L, NP, O	III, IV	Hu (po)	81 mg/kg x 3, weekly during RT	RT	45-75 Gy/4.5-9.5 wks	36/42[a]	NA[†]
EORTC73-OC[84]	1973–75	OP	II-IV	B (im or iv)	15 mg x 2, $wks_{1,2,3,4,5}$	RT	70 Gy/7-8.5 wks	199/226	7.0 [5.7 ; 7.5]
Turku[85]	1975–79	OC, HP, L, O	I-IV	B (im)	7–15 mg x 5, $wks_{1,3}$	RT RT + S	55-60Gy /9 wks, sc 30-32 Gy/3 wks	46/46[b]	18.1 [17.7 ; 21.3]
NRH-78[86]	1978–81	OC, OP, HP, L, NP, O	II-IV	B (im)	5 mg x 2–35	RT, RT+ S	65 Gy/6-7 wks +/- curietherapy	222/222[c]	14.5 [14.1 ; 14.7]
Barcelona[30]	1978–88	OC, HP, L, NP, O	III, IV	F	250 mg/m² every 2d, wks_{1-6}	RT	60 Gy/6 wks	573/600[d]	12.8 [12.3 ; 13.8]
Manchester[87,88]	1979–84	OC, OP, HP, NP, L	I-IV	Mx	100 mg/m², $wks_{1,3}$	RT	45-55 Gy/3 wks	313/313[e]	13.9 [12.5 ; 15.0]
ECOG 2382 [89,90]	1982–87	OC, OP, HP, L, NP, O	I-IV	C	20 mg/m², $wks_{1-7\ or\ 8}$	RT	68-76 Gy/7-8 wks	371/371[f]	15.3 [14.3 ; 16.0]
AC Camargo[39]	1984–86	OC OP, HP	IV	B C	5 mg x 2, $wks_{1,4,7}$ 20 mg/m² x 2, $wks_{1,4,7}$	RT	70 Gy/ 7 wks (Co) or 8 wks (Ex)	60/60[g]	9.6 [2.4 ;]*
Ontario[91]	1987–91	OC, OP, HP, L	III, IV	F	1200 mg/m² x 3, $wks_{1,3}$	RT	66 Gy/6.5 wks	175/175[h]	5.7 [5.3 ; 6.0]
Kragujevac1[35]	1988–91	OC, OP, HP, L, NP	III, IV	$\underline{Arm_1}$: C $\underline{Arm_2}$: Cb	6 mg/m² x 5, wks_{1-7} 25 mg/m² x 5, wks_{1-7}	RT	70 Gy/7-7.5 wks	159/159[i]	4.8 [4.3 ; 5.0]
Bavaria-89[92]	1989–93	OC, OP, HP, L	III, IV	C F LA	60 mg/m², $wks_{1,4,7}$ 350 mg/m² x 1 bolus + x 5 ci, $wks_{1,4,7}$ 50 mg/m² bolus +100 mg/m² x 5 ci, $wks_{1,4,7}$	RT	70.2 Gy/7.3 wks, bid, sc	298/298[j]	1.6 [1.4 ; 2.1]
LOHNG-91[93]	1991–93	OC, OP, HP, O	III, IV	B Mi dicoumarol	5 U x 2, wks_{1-7} 10-15 mg/m² , wks_{1-7}	RT	66-70 Gy/6.5-7 wks	64/64[k]	11.0 [9.3 ; 11.9]
WIA-0C5a[27]	1971–72	OC	III, IV	B (ia)	10–15 mg x 2-3, $wks_{1,2,3,4,5,6,7}$	RT	65 Gy/6.5 wks (Co) 55-60 Gy/6.5-7 wks (Ex)	50/50[l]	23.9 [23.6 ; 23.9]
WIA-0C5b[27]	1972–73	OC	III, IV	B (ia or iv)	10–15 mg x 2-3, $wks_{1,2,3,4,5,6,7}$	RT	65 Gy/6.5wks (Co) 55-60 Gy/6.5-7 wks (Ex)	79/79[l]	21.4 [17.0 ; 22.5]
Bergen[94]	1973–75	OC, OP, L, NP, O	I-IV	B (im)	15 mg $d_{1,3,5}$, $wks_{1,2,3,5}$	RT + S	30 Gy /5 wks, sc	32/32[m]	21.1 [12.0 ; 21.8]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized [µ]	Median follow-up [95% CI] (years)
RT-BLM-73[95]	1973–76	OC	II, III	B (im)	5 mg x 3, $wks_{1,2,3}$	RT	40-50 Gy/4-5 wks (Co) 30 Gy/3 wks (Ex)	46/46[n]	10.7 [10.3 ; 10.8]
WIA-OC5c[27]	1974–75	OC	III, IV	B (im)	10–15 mg x 3, $wks_{1,2,3,4,5+6,7}$	RT	65 Gy/6.5 wks (Co) 55-60 Gy/6.5-7 wks (Ex)	40/40[l]	19.3 [11.7 ; 20.7]
UW-77[49]	1977–78	OC, OP, HP, NP, L	III, IV	A B F Hu (po) Mx (po) Mp (po) Vc	40 mg, $wks_{1,5,10}$ 60 mg, $wks_{1,5,10}$ 500 mg, $wks_{1,5,10}$ 2000 mg, $wks_{1,5,10}$ 30 mg x 3, $wks_{1,5,10}$ 200 mg, $wks_{1,5,10}$ 2 mg, $wks_{1,5,10}$	RT alt	65 Gy/8 wks, sc	58/58[o]	NA[†]
UW-79[50]	1979–80	OC, OP, HP, L, NP	III, IV	B C	10 mg/m² $days_{1,3,5,7}$, $wks_{1,5,9+13,17,21,25,29,33}$ 20 mg/m² $days_{1,3,5}$, $wks_{1,5,9+13,17,21,25,29,33}$	RT alt	48 Gy/5 wks, bid, sc	27/27[p]	NA[†]
Yale-80[96]	1980–86	OC, OP, HP, NP, L	II-IV	Mi	15 mg/m², $wks_{1,7}$	RT S + RT/RT + S	> 56 Gy > 50 Gy	120/120[q]	12.9 [11.7 ; 14.1]
PMHCGS[97]	1982–86	HP, L	I-IV	F (ci) Mi	1000 mg/m² d_{1-4}, $wks_{1,7}$ 10 mg/m², $wks_{1,7}$	RT	50 Gy/4 wks (Co) 50 Gy/8 wks, sc (Ex)	212/212[r]	10.0 [9.2 ; 10.8]
Toulouse[98]	1984–88	OC, OP, HP, L, O	I-IV	C	50 mg x 1, $wks_{1\text{-}7\text{ or }9}$	S + RT	54-70 Gy/6.5-8 wks	90/90[s]	8.9 [7.3 ; 9.0]
SECOG II (unpublished)	1984–89	OC, OP, HP, L, NP, O	III, IV	$\underline{Arm_1}$: B (im) Mx LA (iv) LA (im) Vc $\underline{Arm_2}$: Arm_1 + F	30 mg, $wks_{1,3,6,9}$ 200 mg, $wks_{1,3,6,9}$ 50 mg, $wks_{1,3,6,9}$ 15 mg x 6, $wks_{1,4,6,9}$ 1.5-2 mg, $wks_{1,4,6,9}$ 500 mg, $wks_{1,4,6,9}$	RT alt	60-66 Gy/6.5 wks (Co) 60-66 Gy/8 wks, sc (Ex)	155/155[t]	12.5 [12.1 ; 15.0]
CH-7401[51]	1985–90	OC, OP, HP, L, O	II-IV	F C	1000 mg/m² x4, $wks_{1\ 5,ci}$ 100 mg/m², $wks_{1,5}$	RT S + RT	$\geq$69 Gy/$\geq$6.5, bid, sc 54-60 Gy/5.5-6 wks, bid, sc	62/62[u]	5.9 [5.0 ; 7.6]
Yale-86[99]	1986–92	OC, OP, HP, L, NP, O	I-IV	Mi dicoumarol	15 mg/m², $wks_{1,7}$	RT or S + RT or RT + S	> 56 Gy > 50 Gy	83/83[q]	6.1 [5.0 ; 6.4]
INRC HN-8 [100,101]	1987–90	OC, OP, HP, L, NP	II-IV	F C	200 mg/m² x 5, $wks_{1,4,7,10}$ 20 mg/m² x 5, $wks_{1,4,7,10}$	RT alt	70 Gy/7 wks (Co) 60 Gy/8 wks, alt (Ex)	157/157[v]	5.1 [4.2 ; 5.8]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized [µ]	Median follow-up [95% CI] (years)
First update									
Lucknow 90[52]	1990-91	OC, OP, HP, L	III, IV	Cy Mx F	600 mg/m², $wks_{1,3}$ 60 mg/m², $wks_{1,3}$ 600 mg/m², $wks_{5,6,7,8}$	RT	70 Gy/7 wks starting wk_5	38/38[£]	4.8 [4.6 ; 5.0]
RPC 3250[102]	1990-95	OC, OP, HP, L	III, IV	C (ci) F (ci)	20 mg/m² x 4, $wks_{1,4}$ 1000 mg/m² x 4, $wks_{1,4}$	RT	68-72 Gy/7-8 wks	100/100[£¢]	8.9 [8.2 ; 9.5]
Duke 90040[103]	1990-96	OC, OP, HP, L, NP, O	II-IV	C F	12 mg/m² x 5, $wks_{1,6}$ 600 mg/m² x 5, $wks_{1,6}$	RT	75 Gy/6 wks, bid 70 Gy/7 wks, sc, bid (Ex)	120/122[w]	NA[†]
Vienna[29]	1990-97	OC, OP, HP, L	II-IV	Mi	20 mg/m² d_5	RT	55 Gy/2.5 wks, bid(Co)	158/158[x]	7.9 [6.5 ; 8.9]
UKHAN[42]	1990-2000	OC, OP, HP, L, NP, O	I-IV	Vc B (im) Mx F, alt Mx	1.4 mg/m², $wks_{1,3 \pm 5,7 \text{ or } 8,10}$ 30 mg, $wks_{1,3+5,7 \text{ or } 8,10}$ 100 mg/m², $wks_{1,3 \pm 5,7 \text{ or } 8,10}$ 500 mg/m², $wks_{1,3+5,7 \text{ or } 8,10}$ 100 mg/m², $wks_{1,3}$	RT S + RT	60 Gy/6 wks, alt 50-55 Gy/3-4 wks	966/970[y]	10.1 [9.8 ; 10.5]
Kragujevac2[104]	1991-93	OC, OP, HP, L, NP	III, IV	C	6 mg/m² x 5, wks_{1-7}	RT	77 Gy/7 wks, bid	130/130	6.5 [6.2 ; 6.7]
IAR-92[46]	1992-95	OC, OP, HP, L, O	III, IV	C F FA	20 mg/m²x 4, $wks_{1,4,7,10}$ 300 mg/m² x 4, $wks_{1,4,7,10}$ 20 mg/m² x 4, $wks_{1,4,7,10}$		79.2 Gy/6.5 wks, bid (Co) 80 Gy/9 wks, bid, alt (Ex)	68/68[z]	8.3 [3.9 ; 8.9]
Int 0126[40]	1992-99	OC, OP, HP, L	III, IV	C (Ex1) C (Ex2) F (Ex2)	100 mg/m², $wks_{1,4,7}$ 75 mg/m², $wks_{1,5,9}$ 1000 mg/m² x 4, $wks_{1,5,9}$	RT	70 Gy /7 wks (Co, Ex 1) 60-70 Gy/11-12 wks, sc (Ex2)	295/295[aa]	11.0 [9.4 ; 11.6]
RTOG 9111 [31,32]	1992-2000	OP, L, O	II-IV	C	100 mg/m², $wks_{1,4,7}$	RT	70 Gy/7 wks	366/367[bb]	12.2 [11.2 ; 12.9]
ORO-9301[28]	1993-98	OP	II-IV	Cb F	75 mg/m²x 4, $wks_{1,5,9}$ 1000 mg/m²x 4, $wks_{1,5,9}$	RT	66-70 Gy/7 wks	127/127[cc]	7.0 [5.7 ; 8.1]
GORTEC 9401 [105]	1994-97	OP	III, IV	Cb F	70 mg/m²x 4, $wks_{1,4,7}$ 600 mg/m²x 4, $wks_{1,4,7}$	RT	70 Gy/ 7 wks	226/226	5.3 [4.7 ; 5.7]
ARO 95-06[106]	1994-99	OC, OP, HP	III, IV	Mi F	10 mg/m², $wks_{1,6}$ 600 mg/m² x 5, wk_1	RT	77.6 Gy/ 6 wks, bid (Co) 70.6 Gy/ 6 wks, bid (Ex)	384 /384[dd]	8.8 [7.8 ; 9.4]
EORTC 22931 [107]	1994-2000	OC, OP, HP, L	I-IV	C	100 mg/m² $wks_{1,4,7}$	S + RT	66 Gy/6.5 wks	334/334	5.0 [4.7 ; 5.4]
SAKK 10-94 [108,109]	1994-2000	OC, OP, HP, L	II-IV	C	20 mg/m² x 5, $wks_{1,5}$	RT	74.4 Gy/6.5 wks, bid	224/224	9.7 [8.4 ; 11.4]
Cologne 95[43]	1995-99	OP, HP	II-IV	Cb F	70 mg/m² x 5, $wks_{1,4}$ 600 mg/m² x 5, $wks_{1,4}$	RT	69.9 Gy / 5.5 wks, b	263/263[ee]	4.7 [4.0 ; 5.0]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized [µ]	Median follow-up [95% CI] (years)
HeCOG 9405[36]	1995-99	OC, OP, HP, L	II-IV	C (Ex1) Cb (Ex2)	100 mg/m², wks $_{1,4,7}$ AUC 7, wks $_{1,4,7}$	RT	70 Gy / 7.5 wks	128/128[ff]	14.4 [11.7 ; 14.8]
RTOG 9501 [110,111]	1995-2000	OC, OP, HP, L, O	I-IV	C	100 mg/m² wks$_{1,4,7}$	S + RT	60 Gy/ 6 wks	459/459[gg]	10.2 [9.6 ; 10.8]
EORTC 22954 (unpublished)	1996-99	L, HP	II-IV	C	100 mg/m², wks $_{1,4,7}$	RT	70 Gy/ 7 wks 70 Gy/ 7 wks, bid	59/59[hh]	4.5 [4.1 ; 4.9]
EORTC-22962 (unpublished)	1996-99	OC, OP, HP, L	II-IV	C	100 mg/m², wks $_{1,4,7}$	RT	70 Gy/ 7 wks 80.5 Gy/ 7 wks, bid	57/57[ii]	4.4 [3.6 ; 4.8]
IAEA-MMC[112]	1996-99	OC, OP, HP, L	III, IV	Mi	15 mg/m² d_5	RT	66 Gy /6.5 wks	478/478	2.8 [2.3 ; 3.2]
GORTEC 9601 [113]	1996-2000	OC, OP, HP, L, O	IV	C F	100 mg/m², wks $_{1,3,5}$ 1000 mg/m² x 5, wks $_{1,5}$	RT	62 Gy/ 3 wks, bid (Co) 62 Gy/ 5 wks, bid, sc (Ex)	109/109[ij]	10.9 [6.5 ; 13.3]
NCI-V98-1416 [114]	1997-2000	OC, OP, HP, L	II-IV	Pm	40 mg/m², wks$_{1,7}$	RT	70 Gy/ 7 wks	393/393	0.9 [0.7 ; 1.0]
LOHNG-97[115]	1997-2001	OC, OP, HP, L, O	III, IV	B Mi	5 mg twice-a-week during RT 15 mg/m², wk$_2$	S + RT	56-70 Gy / 5.5-7 wks	114/114	15.4 [14.4 ; 16.2]
Second update									
Torino 85[19]	1985-90	OC, OP, HP, L, NP, O	III, IV	Arm$_1$: B C Mx Vc Arm$_2$: Arm$_1$ + C	 ind: 10 U/m² $d_{1,8,15,22,29,36}$ ind: 50 mg/m² $d_{4,22}$ ind: 40 mg/m² $d_{1,15,22,36}$ ind: 2 mg/m² $d_{1,8,15,22,29,36}$ conco: 5 mg/m² daily during RT	RT	60 Gy/7wks	108/108[kk]	7.2 [6.5 ; 7.9]
Créteil 85[20]	1987-90	OC, OP, HP, L	II-IV	Arm$_1$: C F (ci) Arm$_2$: Arm$_1$ + C F (im)	ind: 100 mg/m², wks $_{1,4,7}$ ind: 1000 mg/m² x 5, wks $_{1,4,7}$ conco: 50 mg/m² $d_{1,15,29,43}$ conco: 5 mg/kg , three time a week during RT	RT	70 Gy/8 wks	56/57[ll]	5.3 [4.3 ; 6.5]
Torino 92[116]	1992-95	OC, OP, HP, L	III, IV	Cb	45 mg/m² x 5, wk$_{1,3,5,7}$	RT	70 Gy/7 wks	151/164	13.6 [12.9; 19.8]
Lucknow 95[37]	1995–99	OC, OP, HP, L, O	III, IV	C	35 mg/m², wks$_{1-7}$	RT	70 Gy/7 wks	200/200 [µµ]	13.0 [10.4; 14.5]
AIIMS 2003[117]	2003-05	OP, NP	III, IV	C	40 mg/m², wk$_{1-7}$	RT	70 Gy/7 wks	176/176	3.0 [2.4 ; 4.8]
BiRCF[118]	1997-2002	OC, OP, HP, L	III, IV	C F F	100 mg/m², wks $_{1,4,7}$ 750 mg/m² x 5, wks $_1$ 430 mg/m² x 5, wks$_{4,7}$	RT	80.4 Gy/7 wks, bid	171/171[mm]	6.6 [6.0 ; 7.1]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized [µ]	Median follow-up [95% CI] (years)
FCRT 94[119]	1994-2002	OP, HP, L	I–IV	Cb	50 mg/m² $d_{1,3}$ weekly during RT	S + RT	54 Gy/6.5 wks or 72 Gy/8 wks	144/146[nn]	8.9 [7.4 ; 10.0]
UPCI 93-99[120]	1994-2002	OP, HP, L	III, IV	Cb	100 mg/m² weekly during RT	S + RT	59.4 Gy/6.5 wks	76/76[oo]	6.2 [5.2 ; 9.9]
TMH 1114[24]	2000–2008	OP, HP, L	II–IV	C	30 mg/m² wks_{1-7}	RT	66-70 Gy/6-7 wks	131/NA[pp]	4.5 [2.0 ;7.8]

* Upper value not reached

[†] Median follow-up and 95% confidence interval not available of high rate of mortality.

[µ] Number of patients analyzed in the meta-analysis and corresponding number of patient randomized.

A: Doxorubicin ; AC Camargo: Hospital AC Camargo ; AIIMS: All India Institute of Medical Sciences ; alt: alternating ; ARO: Arbeitsgemeinschaft für Radio-Onkologie ; b: boost ; B: Bleomycin ; bid: twice daily ; BiRCF: Bifractionnated Radiotherapy and cisplatin/5-fluorouracile ; C: Cisplatin ; Cb: Carboplatin ; CH: Chapel Hill ; ci: continuous infusion ; Cy: Cyclophosphamide ; conco: concomitant ; Co: Control arm ; d: day ; ECOG: Eastern Cooperative Oncology Group ; EORTC: European Organisation for Research and Treatment of Cancer ; F: 5-Fluorouracil ; Ex: Experimental arm; FCRT: French Carboplatine Radiotherapy Trial ; GORTEC: Groupe d'Oncologie Radiothérapie Tête Et Cou ; HeCOG: Hellenic Cooperative Oncology Group ; HP: Hypopharynx ; Hu: Hydroxyurea ; ia: intrarterial ; IAEA-MMC: International Atomic Energy Agency – Mitomycine ; IAR: Instituto de Oncologia Angel H. Roffo ; im: intramuscular ; ind: induction ; INRC-HN: Instituto Nazionale per la Ricerca sul Cancro-Head and Neck ; INT: US INTer group trial ; iv; intravenous ; L: Larynx ; LA: Leucovorina Acid ; LOHNG: Ljubljana Oncology Head and Neck Group ; MDA: MD Anderson ; Mi: Mitomycin ; Mp: Mercaptopurine ; Mx: Methotrexate ; NA: Not Available ; NCI-V: National Cancer Institute ; NP: Nasopharynx ; NRH: Norwegian Radium Hospital ; O: Other ; OC: Oral Cavity ; OP: Oropharynx ; ORO: Oropharynx ; Pm: Porfiromycin ; po: per os ; PMHCGS: Princess Margaret Hospital Cooperative Group Study ; RPC: Research Program Committee ; RT: Radiotherapy ; RTOG: Radiation Therapy Oncology Group ; RT-BLM: Radiotherapy – Bleomycin ; S: Surgery ; SAKK: Swiss Group for Clinical Cancer Research ; sc: split course ; SECOG: South of England Co-operative Oncology Group ; TMH: Tata Memorial Hospital ; UKHAN: United Kingdom Head And Neck ; UPCI: University of Pittsburgh Cancer Institute ; UW: University of the Witwatersrand ; Vc: Vincristine ; WIA-OC: Cancer Institute (WIA) Oral Cavity ; wks: weeks

[a] Randomization 3:2. For patients with extensive disease, treatment duration was 8-9 weeks with 8.5 Gy by week. There were 10 patients (4 and 6 in control and experimental arm respectively), with recurrence after surgery or radiotherapy, who were treated by 50-60 Gy in 5-6 weeks.

[b] Preoperative radiotherapy and decision about surgery after 30 Gy. Surgery omitted in 21 patients (advanced age: 11; poor general condition: 6; refusal: 4). After an interval of 3 weeks, they received an additional course of radiotherapy up to a total dose of 55-60 Gy.

[c] Average dose for external radiotherapy, dose was superior to 70 Gy in 145 patients (74 in control arm and 71 in the experimental arm). Curietherapy using Iridium 192 was given to 46 patients with residual tumour after radiotherapy (27 in control arm and 19 in the experimental arm, average dose 26 and 23 Gy respectively). Surgery was performed after radiotherapy was in 102 patients with residual tumour (55 in control arm and 47 in the experimental arm; including neck dissection only in 10 and 6 patients respectively). Four patients had surgery before radiotherapy (2 in each arm). Bleomycin was injected before each irradiation treatment but was discontinued frequently because of excessive mucositis or other reaction, average dose 104 mg (range 10-175).

[d] Third-arm not eligible (bifractional radiotherapy) with 859 patients overall.

[e] 45-55 Gy (87% $\geq$ 50Gy) in 15-16 fractions over 3 weeks. Methotrexate $d_{0,14}$ with folinic acid rescue if methotrexate concentration greater than 0.4 µmol/L.

[f] 68-78 Gy with fraction of 1.8-2Gy, 5 days a week. In the experimental arm, only 1.8 Gy/fraction.

[g] Three-arm trial with an induction arm and 90 patients overall, see table on induction trial for detail.

[h] Saline infusion in control arm.
[i] Three-arm trial with two chemotherapy arms.
[j] Three series of 23.4 Gy in 13 fractions twice daily (1.8 Gy/fractions) separated by a rest period of 11 days, total dose of 70.2 Gy in 51 days.
[k] Bleomycin: 5 units twice a week with the planned total dose of 70 units; mitomycin: 15 mg/m² after 9-10 Gy and 10 mg/m² on the last day of radiotherapy.
[l] In control arm, radiotherapy of 65 Gy in 6.6-7 weeks with 10 Gy in 5 day a week; in experimental, the severity of mucosal reaction compelled into 3 day a week with 6-7.5 Gy, the total dose was 55-60 Gy in 6.5-7 weeks. The ia and iv cases received 10-15mg of the bleomycin twice or three times a week, depending upon the intensity of the oral mucosal reaction to a total dose of 150-250 mg. The im cases received 30 mg of bleomycin twice a week for two weeks, the radiation commencing two weeks after the first injection on a three fraction per week basis. Another 30 mg were injected during radiation to a total dose of 150 mg. The control arm received a placebo (distilled water).
[m] 30 Gy preoperative, 1.5 Gy (5 days a week) on $weeks_{1,2,4,5}$, one week rest on $week_3$; bleomycine or placebo intramuscular during radiotherapy.
[n] 2 Gy per fraction, 5 times a week: total dose 40-50 Gy in control arm and 30 Gy in experimental arm. Dose of bleomycin was usually 45-60 mg.
[o] 2.5 Gy/fraction, two series of 32.5 Gy in 17 days with 3 weeks rest; in the experimental arm, radiotherapy stated at d_7 with first cycle of chemotherapy at day_0, second cycle at day_{28} (midway rest period) and third one at day_{63} one week after the end of radiotherapy.
[p] 2.4 Gy twice a day for 5 days, two series separated by 24 days rest period, same in both arms; chemotherapy: 3 cycles plus 6 other cycles if responding or stable disease.
[q] In excess of 56 Gy for radical radiotherapy (mean dose received 68 Gy) or postoperative radiotherapy with residual disease (mean dose received 60 Gy) with one injection of mitomycin C in day_5 and another 6 weeks later in the experimental arm; in excess of 50 Gy (mean dose received 58 Gy) for preoperative radiotherapy (n=3) or postoperative radiotherapy without residual disease with one injection of mitomycin C in day_5 in the experimental arm; 1.8-2 Gy/fraction, 5 days a weeks.
[r] In control arm: 50 Gy in 20 fractions over 4 weeks; in experimental arm: 25 Gy in 10 fractions over 2 weeks, rest of 4 weeks, and a second series of 25 Gy in 10 fractions over 2 weeks.
[s] In case of negative margin: 54 Gy, 1.7 Gy/fraction, 5 days a week; in case of positive margin: 65-70 Gy with fraction of 1.8/2 Gy after 54 Gy; 7 to 9 weekly cisplatin injection in the experimental arm.
[t] Three-arm trial with an induction arm and 239 patients overall; in the control arm: radiotherapy of 60-66 Gy, 5 days a week with fraction of 1.8-2 Gy (recommended fractionation); in the experimental arm: one cycle of chemotherapy on $days_{1,2,3}$, two weeks of radiotherapy (starting at day_4), second cycle of chemotherapy, one week rest, two weeks of radiotherapy, third cycle of chemotherapy, one week rest, two weeks of radiotherapy, fourth cycle of chemotherapy. Patients allocated to the chemotherapy arms were also randomized initially to receive B/Mx/Vb or the same chemotherapy plus F, and after July 1st, 1986 received all B/Mx/Vb/F.
[u] For the resectable group, 1.5 Gy twice a day for 10 days, 2 weeks rest, 1.5 Gy for 8-13 days, 5 days a week; 54 Gy for resected group with negative margin, and 60 Gy for resected group with positive margin. The minimum dose was 69 Gy for the unresectable group.
[v] In the experimental arm, Three series of 20 Gy, 2 Gy/fraction, 5 days a week, during $weeks_{2,3,5,6,8,9}$ alternating with 4 cycles of chemotherapy during $weeks_{1,\ 4,7,10}$.
[£] Short induction chemotherapy followed by concomitant chemotherapy. Trial classified as concomitant in all the analyzes.
[££] After 55 Gy, patients were reevaluated. Those with a clinical response completed radiotherapy. Radiation was discontinued in case of non-response or progression. Surgical resection was recommended for those patients.
[w] Seven-day interruption in the experimental arm after 40 Gy and lower total dose to the primary tumor. Two other cycles after of all local therapy: same dose of 5-Fluorouracil, 80 mg/m²/weeks of cisplatin for the third cycle, and 100/m²/weeks for the fourth.
[x] Three-arm trial and 239 patients overall, third arm excluded (conventional radiotherapy).
[y] Trial originally designed for stages II-IV but a few (n<10) T1N0 patients were included. 2x2 factorial design with randomization 3:2:2:2 for patients without previous surgery (n=713): radiotherapy alone, radiotherapy + simultaneous chemotherapy, radiotherapy followed by subsequent chemotherapy, radiotherapy + both. If prior surgery (n=253 patients), patients randomized (3:2) to radiotherapy alone vs. radiotherapy + simultaneous chemotherapy. Each centre chose one option from the following: radiotherapy at 50-55 Gy over 3 weeks with methotrexate alone; radiotherapy at 60 Gy over 6 weeks with either methotrexate alone or VBMF. Another regimen was also used: 55 Gy given in 20 fractions (2.75 Gy per fraction) over 4 weeks. 50 Gy given in 20 fractions (2.5 Gy per fraction) was given postoperatively. Chemotherapy was given on $weeks_{1,3}$ in the

simultaneous arm. For the subsequent arm, chemotherapy was given on weeks$_{2,4}$ after the end of radiotherapy (weeks$_{5,7}$ for 50-55 Gy over 3 weeks; or weeks$_{8,10}$ for 60 Gy over 6 weeks). The VBMF regimen includes vincristine, bleomycin, 5-fluorouracil, methotrexate with folinic acid rescue.

[z] Radiotherapy alternating with chemotherapy: 80 Gy, 2 Gy/day on weeks$_{2\text{-}3}$, 1.5 Gy twice a day on weeks$_{5,6,8,9}$; randomization 2:1.

[aa] Three-arm trial: conventional radiotherapy, conventional radiotherapy + cisplatin (100 mg/m², Ex1), split course radiotherapy (5 weeks rest) with cisplatin (75 mg/m²) + 5-Fluorouracil (Ex2).

[bb] Three-arm trial with 547 patients overall: conventional radiotherapy, radiotherapy + concomitant cisplatin, larynx preservation arm with first 2-3 cycles of cisplatin + 5-Fluorouracil and then, according to the tumor response, radiotherapy or radiotherapy + surgery; the third arm was not eligible for this meta-analysis.

[cc] Three-arm trial and 192 patients overall, third arm excluded (hyperfractionated radiotherapy).

[dd] Experimental arm.

[ee] Second randomization, prophylactic G-CSF or not; weeks$_{1,2,3}$, 1.8 Gy daily, weeks$_{4,5,6}$ bid, 1.8/1.5 Gy daily.

[ff] Three-arm trial: radiotherapy alone, radiotherapy + cisplatin, radiotherapy + carboplatin.

[gg] With a boost of 6 Gy in 3 fractions over a period of three days to high-risk sites.

[hh] Centers chose between conventional or bifractionated radiotherapy, and between evaluation at 2 months after completion of radiotherapy with salvage surgery if patients were not complete responders (option 1) or evaluation after 40-50 Gy (4-5 weeks). In this second case (option 2), the radiotherapy was complete up to 70 Gy if partial response or complete response. If not, surgery was performed. As in option 1, an evaluation was planned 2 months after completion of radiotherapy with salvage surgery if no complete response.

[ii] 2x2 factorial design.

[jj] One week rest after each week of radiotherapy (2 breaks of one week); concomitant arm 2 more cycles (PF) after radio-chemotherapy if complete response.

[kk] 2 Gy /fraction, 10 Gy/wk

[ll] 1.8 Gy fraction

[μμ] Three-arm trial with an induction arm and 300 patients overall

[mm] 1.2 Gy/fraction

[nn] This study included patients who had received chemotherapy before surgery: 18 patients in the control arm and 25 in the experimental arm. The type of induction chemotherapy was left to the physician's discretion. Patients were randomized after surgery. For patients with negative resection margins, 54 Gy, 1.8 Gy by fraction, in 30 fractions, and for patients with positive margins 72 Gy. The trial was stopped prematurely after publication of the preliminary results of the EORTC 22931 trial.

[oo] For clinically uninvolved areas, the dose delivered was 50.4 Gy in 28 fractions of 1.80 Gy per day. Regions that were at high risk received additional boost, usually 9 Gy (total tumor bed dose, 59.4 Gy) in five fractions, but higher boost doses were allowed at the radiation oncologist's discretion. The trial stopped early because of low accrual.

[pp] 2 Gy per fraction once daily, five times per week (total 33–35 fractions). Three-arm trial with 199 overall and a third arm evaluating moderately accelerated radiotherapy: same dose and number of fraction, but 6 fractions a week instead of 5. The trial was stopped early because of poor accrual.

Web-Table 3: Description of adjuvant trials

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ Randomized[u]	Median follow-up [95% CI] (years)
Initial meta-analysis									
Pitié 74[33]	1974–77	OC	II-IV	B (im) Mx LA (im)	15 mg x2, weekly x 15 400 mg, monthly x 24 100 mg, monthly x 24	S or S + RT	MD MD	96/96[a]	5.6 [4.5 ; 6.5]
GETTECadj [121]	1982–85	OC, OP, HP, L, NP	I-IV	B B (im) C Mx	15 mg x3, $wks_{1, 4, 7}$ then 15 mg $d_{1,15}$, monthly x 5 150 mg, $wks_{1, 4, 7}$ 100 mg, $wks_{1, 4, 7}$, then monthly x 5	S + RT	50 Gy/5 wks	286/286[b]	8.9 [8.3 ; 9.2]
Int 0034[122]	1984–89	OC, OP, HP, L, NP	II- IV	C F	100 mg/m^2, $wks_{1, 4, 7}$ 1000 mg/m^2 x 5, $wks_{1, 4, 7}$	S + RT	50-54 Gy/5-6wks	499/499[c]	8.2 [7.9 ; 8.8]
JHCFUS[123]	1985–86	OC, OP, HP, L, NP, O	I-IV	Hc (po)	300–600 mg x 84 d+	S	NA	191/191	2.9 [2.8 ; 3.0]
TMH R4[124]	1986–89	OC	III, IV	Mx	50 mg/m^2 $d_{3,10,17}$ post-operative	S	NA	135/135	1.3 [1.1 ; 1.6]
KKD-86[125]	1986–89	OC	I-IV	U (po)	400 mg d_{1-365}	S	NA	112/112	6.9 [6.4 ; 7.3]
HNU-87a[26]	1987–90	OC, OP. HP, L, NP	I-IV	U (po)	300 mg d_{1-365}	RT	MD	111/111	4.1 [3.8 ; 4.4]
HNU-87b[26]	1987–90	OC, OP, HP, L, NP	II-IV	U (po)	300 mg d_{1-365}	S	NA	424/424	4.2 [4.0 ; 4.3]
First update									
UKHAN[42]	1990-2000	OC, OP, HP, L, NP, O	I-IV	Vc B Mx F, alt Mx	1.4 mg/m², $wks_{1,3,+5,7,or\ 8,10}$ 30 mg im, $wks_{1,3,+5,7,or\ 8,10}$ 100 mg/m², $wks_{1,3,+5,7,or\ 8,10}$ 500 mg/m², $wks_{1,3,+5,7,or\ 8,10}$ 100 mg/m², wks $_{1,3,+5,7,or\ 8,10}$	RT	60 Gy/6 wks, alt 50-55Gy/3-4 wks	966/970[d]	10.1 [9.8 ; 10.5]
Second update									
HNCP[38]	1978–82	OC, HP, L	II- IV	B (bolus) B (ci) C C	ind: 15 mg/m² d_3 ind: 15 mg/m² d_{3-7} ind: 100 mg/m² d_1 adj: 80 mg/m² monthly, x 6	S + RT	50 Gy/5-5.5wks	302/302[e]	5.3 [5.1 ; 5.5]
DFCI[21]	1980-83	OC, OP, HP, L, NP, O	III, IV	B (ci) C Mx LA	ind: 10 U/m² d_{3-7}, $wks_{1,5}$ ind: 20 mg/m² x 5, $wks_{1,5}$ ind: 200 mg/m² $d_{15,22}$, $wks_{1,5}$ ind: 80 mg po, $d_{16-18,23-25}$, $wks_{1,5}$	RT	68 Gy/8wks	46/46[f]	9.9 [8.3 ; 10.7]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ Randomized[µ]	Median follow-up [95% CI] (years)
				B C Mx LA	adj: 10 U/m² d_{2-4}, three 42-days cycles adj: 20 mg/m² d_{1-3}, 3 cycles adj: 200 mg/m² $d_{15,22,29,36}$, 3 cycles adj: oral rescue	or S + RT	60 Gy		

adj : Adjuvant ; alt: alternating ; B: Bleomycin ; C: Cisplatin ; d: Day ; DFCI: Dana–Farber Cancer Institute ; DM: Data Missing; F: 5-Fluorouracil ; GETTEC: Groupe d'Etude des Tumeurs de la Tête Et du Cou ; Gy: Gray ; Hc: Hexycarbanoyl 5-fluorouracil ; HNCP: Head and Neck Contract Program ; HNU: Head and Neck UFT ; HP: Hypopharynx ; im: Intramuscular ; ind: Induction ; INT: US INTer group trial ; JHCFUS: Japanese H C F U Study ; KKD: Kanto Koshinetsu District ; L: Larynx ; LA: leucovorin ; Mx: Methotrexate ; NA: Not Applicable ; NP: Nasopharynx ; O: Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per-os ; RT: Radiotherapy ; S: Surgery ; TMH: Tata Memorial Hospital ; U: UFT (tegafur + uracil) ; UKHAN: United Kingdom Head And Neck ; Vc: vincristine ; wks: weeks

[a] Third arm with immunotherapy ineligible. 23 patients were treated by surgery + radiotherapy. Data on the modality of radiotherapy are not available.
[b] All patients had positive nodes and capsular rupture, 50 Gy on node with overdosage of 15 Gy on area with capsular rupture. CT started 8 weeks after radiotherapy.
[c] 50-54 Gy for low risk and 60 Gy for high risk, 1.8-2 Gy per fraction, 5 days a week.
[d] Four-arm trial for patients without previous surgery (n=713): radiotherapy alone, radiotherapy + simultaneous chemotherapy, radiotherapy followed by subsequent chemotherapy, radiotherapy + both (2x2 factorial design). If prior surgery (n=253 patients), randomized to radiotherapy alone vs. radiotherapy + simultaneous chemotherapy. Only patients receiving subsequent chemotherapy are included in the adjuvant timing part. Each center chose one option from the following: radiotherapy 50-55 Gy/3 weeks with Mx alone; radiotherapy 60 Gy/6 weeks with either Mx alone or VBMF. Another regimen was also used: 55 Gy given in 20 fractions (2.75 Gy per fraction) over 4 weeks. Chemotherapy is given at weeks 1 and 3 for the simultaneous arm. For the subsequent arm, chemotherapy is given weeks 2 and 4 after end of radiotherapy (weeks 5 and 7 for 50-55 Gy/3 weeks; or weeks 8 and 10 for 60 Gy/6 weeks). The VBMF regimen includes Vc, B, F, Mx with FA rescue.
[e] Induction chemotherapy in both arms and adjuvant radiotherapy randomized: 302 patients included in this comparison. Third arm (160 patients) with loco-regional treatment only not included here. Dose increase to 60 Gy for any area of suspected microscopic residual disease and 70 Gy in know areas of gross residual disease.
[f] Induction chemotherapy in both arms. Patients were randomized after loco-regional treatment. ut of 46 patients, 29 were treated by surgery and radiotherapy and 17 by radiotherapy alone. For postoperative radiotherapy, a minimum of 60 Gy were delivered. For radical radiotherapy, a minimum of 68 Gy in 1.8 to 2.0 Gy fractions were delivered. Radiotherapy was usually completed within 8 weeks.

Web-Table 4: Description of trials comparing induction (sequential) chemotherapy plus radiotherapy to concomitant (alternating) radio-chemotherapy

Trial	Inclusion period	Sites	Stage	Timing	Drug	Chemotherapy	Radiotherapy	Patients analyzed/ randomized	Median follow-up [95% CI] (years)
SECOG I[126]	1980-84	OC, OP, L, O	III, IV	$\underline{Arm_1}$: CT-CT-RT-CT-CT $\underline{Arm_2}$: (CT-RT) x3 - RT	B Mx LA LA (im) Vc	30 mg 200 mg 50 mg 45 mg 2 mg	60-66 Gy/6.5 wks 60-66 Gy/8 wks alt	267/270	19.8 [18.4;20.9]
Brescia[127]	1981-83	OC, OP, HP, NP	III, IV	$\underline{Arm_1}$: CT-CT-CT-CT-RT $\underline{Arm_2}$: RT1-CT-CT-CT-CT-RT2	B Hu (po) Mx LA	15 mg/m² 6000 mg/m² 50 mg/m² 45 mg/m²	64 Gy/4 wks 60 Gy sc	55/56	8.2 [6.4;8.6]
INRC-HN-7[128]	1983-86	OC, OP, HP, L, NP	III, IV	$\underline{Arm_1}$: CT-CT-CT-CT-RT $\underline{Arm_2}$: CT - (CT-RT) x3	B (im) Vb Mx LA	30 U, d_1 6 mg/m², d_1 200 mg, d_2 45 mg, d_3	60-70 Gy 60 Gy, alt	116/116	4.3 [3.1;5.5]
SECOG II (unpublished)	1984-89	OC, OP, HP, L, NP, O	III, IV	$\underline{Arm_1}$: CT-CT-RT-CT-CT $\underline{Arm_2}$: (CT-RT) x3 - CT	B Mx LA (im) Vc F	30 mg 200 mg 90 mg 2 mg/m² 500 mg	60-66 Gy/6.5 wks 60-66 Gy/8 wks alt	160/160*	15.0 [12.3;17.0]
ICC-PCP[129]	1984-91	OC, OP, HP, L, NP, O	III, IV	$\underline{Arm_1}$: CT-CT-CT-RT $\underline{Arm_2}$: (CT-RT) x7	$\underline{Arm_1}$: C F $\underline{Arm_2}$: C F	100 mg/m², d_1 1000 mg/m² x 5 60 mg/m², d_1 800 mg/m² x 5	70 Gy/7 wks 70Gy/13 wks, alt	215/215†	6.0 [5.3;6.6]
CMGH-85 [130,131]	1985-88	OC, OP, HP, NP	II-IV	$\underline{Arm_1}$: CT-CT-CT-RT $\underline{Arm_2}$: CRT-CT-CRT-CT	$\underline{Arm_1}$: C F $\underline{Arm_2}$: C F	100 mg/m², d_1 1000 mg/m² x 5 75 mg/m², d_1 800 mg/m² x 5	60 Gy 60 Gy, sc	48/48	5.8 [5.1;6.5]

Trial	Inclusion period	Sites	Stage	Timing	Drug	Chemotherapy	Radiotherapy	Patients analyzed/ randomized	Median follow-up [95% CI] (years)
Second update									
Lucknow 95[37]	1995–99	OC, OP, HP, L, O	III, IV	Arm1: CT-RT Arm2 CRT	C C	35 mg/m² d_1, wks_{1-7} 35 mg/m² d_1, wks_{1-7}	70 Gy/7 wks	200/200 μμ	13.0 [10.4; 14.5]
EORTC 24954[3,4]	1996-2004	HP, L	II-IV	Arm_1: CT-RT Arm_2: (CT-RT) x3 - CT	Arm_1: C F Arm_2: C F	100 mg/m², d_1 1000 mg/m² x 5 20 mg/m² x 5 200 mg/m² x 5	Arm_1: 70 Gy/7 wks Arm_2: 20 Gy/2 wks x3	450/450 ††	9.0 [8.9;9.0]

B: Bleomycin ; C: Cisplatin ; CMGH: Cleveland Metropolitan General Hospital ; CRT: Chemoradiotherapy ; CT: Chemotherapy ; d: day ; EORTC: European Organisation for Research and Treatment of Cancer ; F: 5-Fluorouracil ; Gy: Gray ; HP: Hypophraynx ; Hu: hydroyurea; im: intramuscular ; ICC-PCP: Illinois Cancer Council - Paris-Chicago Protocol ; INRC-HN: Instituto Nazionale per la Ricerca sul Cancro-Head and Neck ; L: Larynx ; LA: Leucovorin ; Mx: Methotrexate ; NP: Nasopharynx ; O : Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per os ; RT: Radiotherapy ; SECOG: South of England Co-operative Oncology Group : Vb: Vinblastine ; Vc: Vincristine ; wks: weeks

* 3-arm trial with a third arm without chemotherapy; see tables on induction or concomitant trials for detail on treatment.

† 3 cycles of induction chemotherapy every 3 weeks; "concomitant" chemotherapy and radiation consisted of seven cycles of cisplatin and 5-FU, and radiation 2 Gy on days 1 to 5, delivered every other week.

μμ Three-arm trial with an RT alone arm and 300 patients overall

†† Only 153 patients out of 450 were eligible for the present meta-analysis. Centers have the option to have an interim tumour evaluation after 50 Gy (around day 42) or only after the end of radiotherapy in the concomitant arm. In the sequential arm, an evaluation was planned at day 42 after induction chemotherapy for all patients. Only patients included in centres with tumour evaluation in both arms at 42 days were included. Because of unbalance in long-term follow-up between the two arms in the whole trial, follow-up was censored at 9 years.

Web-Table 5: Trial divisions in treatment comparisons

Trial	Comparisons	
Initial meta-analysis		
WIA-OC5[27]	WIA-OC5a	RT + concomitant CT (intra-arterial) versus RT + placebo
	WIA-OC5b	RT + concomitant CT (intravenous) versus RT + placebo
	WIA-OC5c	RT + concomitant CT (intramuscular) versus RT + placebo
HNCP[38][a]	HNCPneo	Surgery e + RT + induction CT versus surgery + RT
	HNCPneo&adj	Surgery + RT + induction CT + adjuvant CT versus surgery + RT
	HNCP*	Surgery + RT + induction CT + adjuvant CT versus surgery + RT + induction CT
Yale-80[96]	Yale 80	RT + concomitant CT versus RT only
	Yale 80po	Surgery + RT + concomitant CT versus surgery + RT
AC Camargo[39][b]	AC Camargo (ind)	RT + induction CT versus RT only
	AC Camargo (conc)	RT + concomitant CT versus RT only
SECOG II[c] (unpublished)	SECOG IIneo	RT + induction CT (without 5-FU, randomized) versus RT only
	SECOG IIneofr	RT + induction CT (with 5-FU, randomized) versus RT only
	SECOG IIneofnr	RT + induction CT (with 5-FU, no randomiszd) versus RT only
	SECOG IIconc	RT + concomitant CT (without 5-FU, randomized) versus RT only
	SECOG IIconcfr	RT + concomitant CT (with 5-FU, randomized) versus RT only
	SECOG IIconcfnr	RT + concomitant CT (with 5-FU, no randomized) versus RT only
	SECOG II	RT + concomitant CT (without distinction on 5-FU) versus RT + induction CT (without distinction on 5-FU)
GSTTC 86[70,71]	GSTTC 86	RT + induction CT versus RT only (non-operable patients)
	GSTTC 86po	Surgery + RT + induction CT versus surgery + RT (operable patients)
Yale 86[99]	Yale 86	RT + concomitant CT versus RT only
	Yale 86po	Surgery + RT + concomitant CT versus surgery + RT
AHNTG[72]	AHNTG	RT+ induction CT versus RT only or other locoregional treatment than surgery et surgery + RT
	AHNTGsurg	Surgery (± RT) + induction CT versus surgery (± RT) only
HNU-87[26]	HNU-87a	RT + adjuvant CT versus RT only
	HNU-87b	Surgery + adjuvant CT versus surgery only
First update		
UKHAN[42][d]	UKHAN1po1	Surgery + RT + concomitant monoCT versus surgery + RT
	UKHAN1po2	Surgery + RT + concomitant polyCT versus surgery + RT
	UKHAN1npo1	RT + concomitant monoCT versus RT only
	UKHAN1npo2	RT + concomitant polyCT versus RT only
	UKHAN1npo1*	RT + concomitant monoCT + adjuvant CT versus RT + adjuvant CT
	UKHAN1npo2*	RT + concomitant polyCT + adjuvant CT versus RT + adjuvant CT
	UKHAN1a1	RT + adjuvant monoCT versus RT only
	UKHAN1a2	RT + adjuvant polyCT versus RT only
	UKHAN1a1*	RT + concomitant CT + adjuvant monoCT versus RT + concomitant CT
	UKHAN1a2*	RT + concomitant CT + adjuvant polyCT versus RT + concomitant CT

Trial	Comparisons	
Int 0126[40][e]	Int 0126a	RT + concomitant CT (cisplatin) versus RT only
	Int 0126b	RT + concomitant CT (5-FU, cisplatin) versus RT only
EORTC 22954 (unpublished)	EORTC 22954a	Conventional RT + concomitant CT versus conventional RT only
	EORTC 22954b	Hyperfractionated RT + concomitant CT versus hyperfractionated RT only
EORTC 22962 (unpublished)	EORTC 22962a	Conventional RT + concomitant CT versus conventional RT only
	EORTC 22962b	Hyperfractionated RT + concomitant CT versus hyperfractionated RT only
Second update		
FCRT 94[119]	FCRT 94	Surgery + RT + concomitant CT versus surgery + RT
	FCRT 94*	Surgery + RT + induction CT + concomitant CT versus surgery + RT + induction CT
Lucknow 95[37][f]	Lucknow 95 (ind)	RT + concomitant CT versus RT only
	Lucknow 95 (conc)	RT + concomitant CT versus RT only
	Lucknow 95	RT + concomitant CT versus RT + induction CT
TTCC 2002[2][g]	TTCC 2002 PF-	RT + induction CT (PF) + concomitant CT versus RT + concomitant CT
	TTCC 2002 PF+	RT + induction CT (PF) + concomitant CT versus RT + concomitant CT
	TTCC 2002 TPF-	RT + induction CT (TPF, without G-CSF) + concomitant CT versus RT + concomitant CT
	TTCC 2002 TPF+	RT + induction CT (TPF, with G-CSF) + concomitant CT versus RT + concomitant CT

Stars are part of comparison names and do not correspond to footnote below the table.

5-FU: 5-fluorouracil, adj: adjuvant, conc: concomitant, CT: chemotherapy, fr: 5-FU randomized, G-CSF: Granulocyte - *Colony Stimulating Factor*, monoCT: mono chemotherapy, neo: neoadjuvant (induction), nfr: 5-FU non-randomized, npo: non post-operative, PF combination of 5-FU + platin salt, po: post-operative, polyCT: polychemotherapy, surg: *surgery*, RT: radiotherapy, TPF: combination of taxane + 5-FU + platin salt

See Web-Tables 1, 2 and 3 for trial abbreviations

[a] Each arm is duplicated once as this trial is included in two timings (induction with duplication of the control arm, concomitant) (462 patients)
[b] Control arm duplicated once (30 patients)
[c] Each arm is duplicated once as this trial is included in two timings (induction, concomitant) and in the secondary question (239 patients). The control arm of the part that randomized addition of 5-FU is duplicated twice (84 patients, overall 323 patients)
[d] Non-postoperative part of the trial with 2x2 design duplicated once as this trial is included in two timings (concomitant, adjuvant) (713 patients). Same monochemotherapy and polychemotherapy for the two timings (centre option). The concomitant polychemotherapy was alternating with radiotherapy.
[e] Control arm duplicated once (102 patients)
[f] Each arm is duplicated once as this trial is included in two timings (induction, concomitant) and in the secondary question (300 patients)
[g] Control arm duplicated once (128 patients)

Web-Table 6: Characteristics of patients overall and by timing (addition of chemotherapy)

	Timing of chemotherapy						All timings	
	Induction		Concomitant		Adjuvant			
	N	%	N	%	N	%	N	%
Sex								
Male	5951	*84.4*	8663	*81.1*	2375	*81.5*	16989	*82.3*
Female	1056	*15.0*	1688	*15.8*	530	*18.2*	3274	*15.9*
Unknown	47	*0.7*	329	*3.1*	10	*0.3*	386	*1.9*
Age (years)								
< 50	1437	*20.4*	2557	*23.9*	566	*19.4*	4560	*22.1*
[50;60[	2725	*38.6*	3637	*34.1*	1000	*34.3*	7362	*35.7*
[60;70[	2157	*30.6*	3197	*29.9*	925	*31.7*	6279	*30.4*
≥ 70	564	*8.0*	944	*8.8*	376	*12.9*	1884	*9.1*
Unknown	171	*2.4*	345	*3.2*	48	*1.7*	564	*2.7*
Median (IQR)	57 (51;63)		57 (50;64)		58 (52;65)		57 (50;64)	
Performance status								
PS0	1953	*27.7*	3818	*35.8*	1434	*49.2*	7205	*34.9*
PS1	2383	*33.8*	3707	*34.7*	521	*17.9*	6611	*32.0*
PS ≥ 2	459	*6.5*	600	*5.6*	57	*2.0*	1116	*5.4*
Unknown*	2259	*32.0*	2555	*23.9*	903	*31.0*	5717	*27.7*
Primary site								
Oral cavity	2157	*30.6*	2121	*19.9*	933	*32.0*	5211	*25.2*
Oropharynx	2669	*37.8*	3995	*37.4*	504	*17.3*	7168	*34.7*
Larynx	836	*11.9*	2150	*20.1*	738	*25.3*	3724	*18.0*
Hypopharynx	1229	*17.4*	1700	*15.9*	468	*46.1*	3397	*16.5*
Others	88	*1.2*	634	*5.9*	265	*9.1*	987	*4.8*
Unknown	75	*1.1*	80	*0.8*	7	*0.2*	162	*0.8*
T-stage								
T0/Tx/Tis	39	*0.6*	43	*0.4*	34	*1.2*	116	*0.6*
T1	202	*2.9*	504	*4.7*	189	*6.5*	895	*4.3*
T2	1292	*18.3*	1727	*16.2*	885	*30.4*	3904	*18.9*
T3	2932	*41.6*	3808	*35.7*	974	*33.4*	7714	*37.4*
T4	2429	*34.4*	4218	*39.5*	588	*20.2*	7235	*35.0*
Unknown	160	*2.3*	380	*3.6*	245	*8.4*	785	*3.8*
N-stage								
N0	2504	*35.5*	2932	*27.5*	1443	*49.5*	6879	*33.3*
N1	1717	*24.3*	1757	*16.5*	431	*14.8*	3905	*18.9*
N2	1619	*23.0*	3754	*35.2*	259	*8.9*	5632	*27.3*
N3	1065	*15.1*	1442	*13.5*	218	*7.5*	2725	*13.2*
N+ (no details)	0	-	473	*4.4*	319	*10.9*	792	*3.8*
Nx	3	*< 0.1*	0	-	0	-	3	*< 0.1*
Unknown	146	*2.1*	322	*3.0*	245	*8.4*	713	*3.5*
Stage								

	Timing of chemotherapy						All timings	
	Induction		Concomitant		Adjuvant			
	N	***%***	**N**	***%***	**N**	***%***	**N**	***%***
Stage 0	0	-	0	-	2	*0.1*	2	*< 0.1*
Stage I-II	423	*6.0*	587	*5.5*	607	*20.8*	1617	*7.8*
Stage III	2393	*33.9*	2574	*24.1*	967	*33.2*	5934	*28.7*
Stage IV Low	974	*13.8*	2132	*20.0*	226	*7.8*	3332	*16.1*
Stage IV High	3072	*43.6*	4851	*45.4*	740	*25.4*	8663	*42.0*
Stage IV M+	11	*0.2*	14	*0.1*	0	-	25	*0.1*
Stage IV (unspecified)	32	*0.5*	197	*1.8*	125	*4.3*	354	*1.7*
Unknown	149	*2.1*	325	*3.1*	248	*8.5*	722	*3.5*
Smoking status								
Never	177	*2.5*	384	*3.6*	0	-	561	*2.7*
Former	267	*3.8*	1025	*9.6*	0	-	1292	*6.3*
Current	91	*1.3*	1119	*10.5*	0	-	1210	*5.9*
Unknown	6519	*92.4*	8152	*76.3*	2915	*100*	17586	*85.2*
HPV status								
Negative	8	*0.1*	40	*0.4*	0	-	48	*0.2*
Positive	44	*0.6*	3	*< 0.1*	0	-	47	*0.2*
Unknown	7002	*99.3*	10637	*99.6*	2915	*100*	20554	*99.5*
Total	**7054**	***100***	**10680**	***100***	**2915**	***100***	**20649**	***100***

* Overall rate of missing data is 5.4% after exclusion of the 40 comparisons that did not collect performance status: 17 (2070 patients) for induction, 19 (2061 patients) for concomitant and 4 (708 patients) for adjuvant
IQR: interquartile range

Web-Table 7: Number of comparisons and patients in trial subsets

	Comparisons (patients)		
	Induction	**Concomitant**	**Adjuvant**
Type of chemotherapy			
PolyCT - With platin salt	36 (5394)	15 (2042)[b]	3 (831)[e]
PolyCT - Without platin salt	6 (744)	12 (1328)	3 (295)
MonoCT - With platin salt	1 (200)	22 (3562)[c]	1 (302)
MonoCT - Without platin salt	2 (716)[a]	22 (3748)[d]	7 (1487)
Platin salt*			
Cisplatin only	1 (200)	16 (2904)[f]	0
Cisplatin and 5-FU	24 (3643)	10 (1339)[g]	1 (499)
Carboplatin only	0	4 (371)	0
Carboplatin and 5-FU	3 (457)	3 (616)	0
Locoregional treatment			
Surgery only	0	0	4 (862)
Conventional RT	15 (2253)	35 (5386)[i]	0
Hyperfractionated and/or accelerated RT	0	11 (1680)	0
Other RT†	7 (1 318)[h]	10 (1657)[j]	5 (824)
Surgery and RT	12 (2079)	11 (1595)	3 (1087)[l]
Other‡	11 (1404)	4 (362)[k]	2 (142)
Year of accrual start			
< 1980	8 (1936)[m]	13 (1721)[n]	3 (444)
1980-1993	28 (3535)	36 (4833)[o]	11 (2471)[p]
1994-2000	1 (200)	21 (4950)	0
2001-2010	8 (1383)	1 (176)	0
Total	**45 (7054)[q]**	**71 (10680)[r]**	**14 (2915)[s]**

* Comparisons were excluded if neither cisplatin nor carboplatin was administrated or if platin salt was combined with drug other than 5-FU. In the induction timing, comparisons using cisplatin + 5-FU and other drug (taxane or other) were included in the cisplatin + 5-FU groups [2,13,61,63,80-83]. Comparisons were also excluded if it was not possible to separate patients treated by cisplatin and those treated carboplatin.

† Alternating radiotherapy, hypofractionated radiotherapy.

‡ Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery

For event-free survival, number of comparisons (number of patients):
[a] 1 (36), [b] 13 (1 959), [c] 20 (3 324), [d] 21 (3 716), [e] 2 (332), [f] 14 (2 665), [g] 9 (1 283), [h] 6 (638), [i] 32 (5 091), [j] 9 (1 630), [k] 3 (330), [l] 2 (588), [m] 7 (1 256), [n] 11 (1 662), [o] 34 (4 669), [p] 10 (1 972), [q] 44 (6 426), [r] 66 (10 327), [s] 13 (2 416)

5-FU: 5-Fluorouracil, MonoCT: Monochemotherapy, PolyCT: Polychemotherapy, RT: Radiotherapy

Web-Table 8: Cause of death and events for cancer/non-cancer mortality

	Timing of chemotherapy					
	Induction		Concomitant		Adjuvant	
	LRT+CT	LRT	LRT+CT	LRT	LRT+CT	LRT
Cause of death						
Cancer	446 *(12.6%)*	472 *(13.4%)*	1422 *(26.6%)*	1789 *(33.6%)*	167 *(11.7%)*	203 *(13.6%)*
Other	297 *(8.4%)*	297 *(8.4%)*	587 *(11.0%)*	467 *(8.8%)*	77 *(5.4%)*	78 *(5.2%)*
Unknown	1584 *(44.8%)*	1596 *(45.3%)*	1874 *(35.0%)*	1805 *(33.9%)*	533 *(37.4%)*	547 *(36.7%)*
Alive	1207 *(34.2%)*	1155 *(32.8%)*	1465 *(27.4%)*	1271 *(23.8%)*	649 *(45.5%)*	661 *(44.4%)*
Events for cancer/non-cancer mortality*						
Previous failure	452 *(44.4%)*	444 *(43.9%)*	1427 *(44.1%)*	1650 *(50.8%)*	NA	NA
Death caused by cancer without previous failure	29 *(2.8%)*	20 *(2.0%)*	181 *(5.6%)*	238 *(7.3%)*	NA	NA
Death caused by unknown reason without previous failure within 5 years after randomization	19 *(1.9%)*	15 *(1.5%)*	122 *(3.8%)*	112 *(3.4%)*	NA	NA
Total (cancer deaths)	**500** ***(49.1%)***	**479** ***(47.3%)***	**1730** ***(53.5%)***	**2000** ***(61.6%)***	**NA**	**NA**
Death caused by unknown reason without previous failure after 5 years after randomization	7 *(0.7%)*	9 *(0.9%)*	100 *(3.1%)*	55 *(1.7%)*	NA	NA
Death caused by other reason without previous failure	142 *(13.9%)*	162 *(16.0%)*	444 *(13.7%)*	356 *(11.0%)*	NA	NA
Total (non-cancer deaths)	**149** ***(14.6%)***	**171** ***(16.9%)***	**544** ***(16.8%)***	**411** ***(12.7%)***	**NA**	**NA**
Patients alive	370 *(36.3%)*	362 *(35.8%)*	960 *(29.7%)*	838 *(25.8%)*	NA	NA

* Number of events was lower for cancer/non cancer deaths analyzes as several trials were excluded because the cause of death was not available. The analysis on cancer/non-cancer death was not performed for the adjuvant timing as cause of death was missing for 9 out of 14 comparisons.

NA: Not Applicable.

Cause of death is missing for all patients in the 65 following comparisons (9896 patients):

Induction comparisons : AC Camargo [39], BNH-003 (unpublished), BuenosAires [34], CFHNS [76,77], Cologne-88 [78], Creteil-82 [61], Creteil-86 [68,69], Denver-77 [56], EORTC 24771 [55], EORTC78-OCP [57], EORTC 24844 (unpublished), HNCGIC02 [62], HNCGIC03 [63], IGR-65 [53], LasPalma [73], MCW-1 [58,59], MCW-2 [65,66], Pitie-81 [44], Rennes-87 [74], RTOG 6801 [54], SHNG-85 [67], SWOG 8006 [60], Shanghai 2008 [82,83], Songkhla [64];

Concomitant comparisons : AC Camargo (included in two timings) [39], AIIMS-2003 [117], Barcelona [30], Bavaria-89 [92], Bergen [94], CH-7401 [51], FCRT 94 [119], FCRT 94* [119], ECOG 2382 [89,90], EORTC73-OC [84], HNAP-02, INRCHN-8 [100,101], Kragujevac1 [35], LOHNG-91 [93], MDA-70 [45], Manchester [87,88], NRH-78 [86], Ontario [91], PMHCGS [97], RT-BLM-73 [95], Torino-85 [19], Toulouse [98], Turku [85], UW-77 [49], UW-79 [50], WIA-OC5a [27], WIA-OC5b [27], WIA-OC5c [27], Yale-80 [96], Yale-80po [96], Yale-86 [99], Yale-86po [99];

Adjuvant comparisons: DFCI [21], GETTECadj [121], HNU-87a [26], HNU-87b [26], Int 0034 [122], JHCFUS [123], KKD-86 [125], Pitie-74 [33], TMHR-4 [124].

Web-Table 9: Events for event-free survival

	Timing of chemotherapy					
	Induction		Concomitant		Adjuvant	
	LRT+CT	**LRT**	**LRT+CT**	**LRT**	**LRT+CT**	**LRT**
Loco-regional failure	1355 *(42.4%)*	1219 *(38.3%)*	2154 *(41.1%)*	2612 *(50.1%)*	256 *(21.8%)*	315 *(25.4%)*
Distant failure	321 *(10.1%)*	413 *(13.0%)*	398 *(7.6%)*	356 *(6.8%)*	136 *(11.6%)*	172 *(13.9%)*
Loco-regional and distant failures	11 *(0.3%)*	16 *(0.5%)*	128 *(2.4%)*	152 *(2.9%)*	4 *(0.3%)*	12 *(1.0%)*
Death without failure*	586 *(18.3%)*	615 *(19.3%)*	1290 *(24.6%)*	1060 *(20.3%)*	301 *(25.6%)*	265 *(21.4%)*
Failure with unknown location	0	20 *(0.6%)*	85 *(1.6%)*	110 *(2.1%)*	0	0
Total (events)	**2273** ***(71.2%)***	**2283** ***(71.8%)***	**4055** ***(77.3%)***	**4290** ***(82.3%)***	**697** ***(59.3%)***	**764** ***(61.6%)***
Alive without failure	921 *(28.8%)*	897 *(28.2%)*	1190 *(22.7%)*	922 *(17.7%)*	478 *(40.7%)*	477 *(38.4%)*
Total	**3194** ***(100%)***	**3180** ***(100%)***	**5245** ***(100%)***	**5212** ***(100%)***	**1175** ***(100%)***	**1241** ***(100%)***

* includes patients dying from cancer, other cause (including toxicity) and of unknown causes in proportion variable according to timing and trials.

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Web-Table 10A: Sensitivity analyzes for the addition of induction chemotherapy

	LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% IC]
Overall survival Main analysis on all trials: 45 comparisons (7054 patients) ; HR=0.96 [0.90;1.01], p=0.14			
One timing of chemotherapy [a] 37 comparisons (5611 patients)	1931 / 2812	1965 / 2799	0.95 [0.89;1.01] p=0.12
No confounded * [b] 40 comparisons (6466 patients)	2134 / 3258	2139 / 3208	0.97 [0.91;1.03] p=0.26
First inclusion ≥ 1980 [c] 37 comparisons (5118 patients)	1705 / 2577	1713 / 2541	0.95 [0.89;1.02] p=0.13
Sample size > 80 patients [d] 36 comparisons (6561 patients)	2140 / 3278	2204 / 3283	0.95 [0.89;1.00] p=0.07
Follow-up > 5 years [e] 32 comparisons (4801 patients)	1635 / 2398	1672 / 2403	0.96 [0.90;1.03] p=0.24
Without duplicated patients [f] 39 comparisons (6687 patients)	2327 / 3534	2115 / 3153	0.96 [0.90;1.01] p=0.14
Event-free survival Main analysis on all trials: 44 comparisons (6374 patients) ; HR=0.96 [0.90;1.02], p=0.14			
One timing of chemotherapy 36 comparisons (4931 patients)	1831 / 2472	1 819 / 2459	0.97 [0.91;1.03] p=0.32
No confounded * 39 comparisons (5786 patients)	2052 / 2918	2039 / 2868	0.96 [0.90;1.02] p=0.16
First inclusion ≥ 1980 37 comparisons, (5118 patients)	1855 / 2577	1847 / 2541	0.95 [0.89;1.02] p=0.15
Sample size > 80 patients 35 comparisons (5881 patients)	2074 / 2938	2109 / 2943	0.95 [0.89;1.00] p=0.07
Follow-up > 5 years 32 comparisons (4801 patients)	1770 / 2398	1791 / 2403	0.97 [0.91;1.03] p=0.33
Without duplicated patients 39 comparisons (6007 patients)	2273 / 3194	2004 / 2813	0.96 [0.90;1.02] p=0.19

* Trial with a lower dose of radiotherapy or the same dose delivered in a longer time in the chemotherapy arm than in the control arm

[a] Eight comparisons excluded: HNCPneo&adj [38], Budapest 2007 [13], DeCIDE [81], GSTTC 2501 [41,80], TTCC 2002 PF- [2], TTCC 2002 PF+ [2], TTCC 2002 TPF- [2], TTCC 2002 TPF+ [2]

[b] Five comparisons excluded: Denver 77 [56], SECOG IIneo (unpublished), SECOG IIneofr (unpublished), SECOG IIneofnr (unpublished), CFHNS [76,77]

[c] Eight comparisons excluded: IGR-65 [53], RTOG 6801 [54], EORTC 24771 [55], Denver-77 [56], HNCPneo [38], HNCPneo&adj [38], EORTC78-OCP [57], MCW-1 [58,59]

[d] Nine comparisons excluded because sample size of trials less than or equal to 80 patients (40 patients per arm): IGR-65 [53], Denver 77 [56], MCW-2 [65,66], AC Camargo [39], Las Palmas [73], Parma [75], Songkhla [64], HNAP-02 [79], Budapest 2007 [13]

[e] Ten comparisons excluded: RTOG 6801 [54], LasPalmas [73], EORTC78-OCP [57], Créteil-82 [61], EORTC 24844 (unpublished), BNH-003 (unpublished), Songkhla [64], Cologne-88 [78], TTCC 2002 [2], GSTTC 2501 [41,80]

[f] Five control arms excluded: HNCPneo [38], SECOG IIneofr (unpublished), SECOG IIneofnr (unpublished), TTCC 2002 TPF- [2], TTCC 2002 TPF+ [2]

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 10B: Sensitivity analyzes for the addition of concomitant chemotherapy

	LRT + CT (No. events / No. patients)	**LRT** (No. events / No. patients)	**Hazard Ratio [95% IC]**
Overall survival Main analysis on all trials: 71 comparisons (10680 patients) ; HR=0.83 [0.79;0.86], p<0.0001			
One timing of chemotherapy [a] 65 comparisons (10121 patients)	3664 / 5074	3836 / 5047	0.81 [0.78;0.85] p<0.0001
No confounded * [b] 54 comparisons (8759 patients)	3124 / 4416	3228 / 4343	0.83 [0.79;0.88] p<0.0001
First inclusion ≥ 1980 [c] 58 comparisons (8959 patients)	3137 / 4464	3348 / 4495	0.83 [0.79;0.87] p<0.0001
Sample size > 80 patients [d] 51 comparisons (9726 patients)	3506 / 4851	3710 / 4875	0.84 [0.80;0.88] p<0.0001
Follow-up > 5 years [e] 60 comparisons (8294 patients)	3252 / 4116	3405 / 4178	0.83 [0.79;0.87] p<0.0001
Without duplicated patients [f] 68 comparisons (10499 patients)	3883 / 5348	3901 / 5151	0.83 [0.79;0.87] p<0.0001
Event-free survival Main analysis on all trials: 67 comparisons (10457 patients) ; HR=0.80 [0.77;0.84], p<0.0001			
One timing of chemotherapy 63 comparisons (10062 patients)	3896 / 5045	4127 / 5017	0.80 [0.76;0.83] p<0.0001
No confounded * 50 comparisons (8536 patients)	3260 / 4313	3410 / 4223	0.80 [0.76;0.84] p<0.0001
First inclusion ≥ 1980 56 comparisons (8795 patients)	3325 / 4390	3579 / 4405	0.79 [0.76;0.83] p<0.0001
Sample size > 80 patients 50 comparisons (9618 patients)	3717 / 4805	3951 / 4813	0.81 [0.77;0.85] p<0.0001
Follow-up > 5 years 56 comparisons (8071 patients)	3280 / 4013	3463 / 4058	0.81 [0.77;0.85] p<0.0001
Without duplicated patients 64 comparisons (10276 patients)	4055 / 5245	4123 / 5031	0.80 [0.76;0.84] p<0.0001

* Trial with a lower dose of radiotherapy or the same dose delivered in a longer time in the chemotherapy arm than in the control arm

[a] Six comparisons excluded: Torino 85 [19], Creteil 85 [20], Lucknow 90 [52], UKHAN1npo1* [42], UKHAN1npo2* [42], FCRT 94* [119]

[b] Seventeen comparisons excluded: WIA-OCa [27], WIA-OCb [27], WIA-OCc [27], RT-BLM73 [95], PMHCGS [97], SECOG IIconc (unpublished), SECOG IIconcfr (unpublished), SECOG IIconcfnr (unpublished), INRC HN-8 [100,101], Duke 90040 [103], UKHAN1npo2 [42], UKHAN1npo2* [42], UKHAN1po2 [42], IAR 92 [46], Int 0126b [40], ARO 95-6 [106], GORTEC 9601 [113]

[c] Twelve comparisons excluded: MDA-70 [45], WIA-OC5a [27], WIA-OC5b [27], EORTC73-OC [84], Bergen [94], RT-BLM-73 [95], WIA-OC5c [27], Turku [85], UW-77 [49], NRH-78 [86], Barcelona [30], UW-79 [50], Manchester [87,88]

[d] Twenty comparisons excluded because sample size of trials less than or equal to 80 patients (40 patients per arm): MDA-70 [45], WIA-OC5a [27], WIA-OC5b [27], Bergen [94], RT-BLM-73 [95], WIA-OC5c [27], Turku [85], UW-77 [49], UW-79 [50], AC Camargo [39], CH-7401 [51], LOHNG-91 [93], Creteil-85 [20], Lucknow-90 [52], IAR-92 [46], UPCI 93-99 [120], EORTC 22954a (unpublished), EORTC 22954b (unpublished), EORTC 22962a (unpublished), EORTC 22962b (unpublished)

e Eleven comparisons excluded: TMH 1114 [24], Cologne-95 [43], Bavaria-89 [92], Kragujevac1 [35], IAEA-MMC [112], EORTC 22931 [107], NCI-V98-1416 [114], Lucknow-90 [52], AIIMS 2003 [117], EORTC 22954 (unpublished), EORTC 22962 (unpublished)

[f] Three control arms excluded: SECOG IIconcfr (unpublished), SECOG IIconcfnr (unpublished), Int 0126a [40]

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 10C: Sensitivity analyzes for the addition of adjuvant chemotherapy

	LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% IC]
Overall survival Main analysis on all trials: 14 comparisons (2915 patients), HR=1.02 [0.92;1.13] ; p=0.69			
One timing of chemotherapy [a] 10 comparisons (2247 patients)	551 / 1090	607 / 1157	1.01 [0.90;1.13] p=0.92
No confounded *, [b] 13 comparisons (2824 patients)	742 / 1382	791 / 1442	1.01 [0.91;1.12] p=0.84
First inclusion ≥ 1980 [c] 11 comparisons (2471 patients)	642 / 1196	691 / 1275	1.06 [0.95;1.18] p=0.32
Sample size > 80 patients [d] 13 comparisons (2869 patients)	762 / 1400	812 / 1469	1.03 [0.94;1.14] p=0.50
Follow-up > 5 years [e] 10 comparisons (2054 patients)	684 / 994	720 / 1060	1.05 [0.95;1.17] p=0.35
Event-free survival Main analysis on all trials: 13 comparisons (2416 patients), HR=0.98 [0.88;1.09] ; p=0.72			
One timing of chemotherapy 9 comparisons (1748 patients)	458 / 839	532 / 909	0.97 [0.85;1.10] p=0.60
No confounded* 12 comparisons (2325 patients)	662 / 1131	726 / 1194	0.98 [0.88;1.09] p=0.66
First inclusion ≥ 1980 10 comparisons (1972 patients)	545 / 945	616 / 1027	1.01 [0.90;1.14] p=0.82
Sample size > 80 patients 12 comparisons (2370 patients)	682 / 1149	748 / 1221	1.00 [0.90;1.11] p=0.96
Follow-up > 5 years 9 comparisons (1555 patients)	551 / 743	591 / 812	1.03 [0.92;1.16] p=0.58

* Trial with a lower dose of radiotherapy or the same dose delivered in a longer time in the chemotherapy arm than in the control arm

[a] Four comparisons excluded: DFCI [21], HNCP* [38], UKHAN1a1* [42], UKHAN1a2* [42]

[b] One comparison excluded: UKHAN1a2* [42]

[c] Three comparisons excluded: Pitie-74 [33], DFCI [21], HNCP* [38]

[d] One comparison excluded because sample size of trials less than or equal to 80 patients (40 patients per arm): DFCI [21]

[e] Four comparisons excluded: HNU-87a [26], HNU-87b [26], TMHR-4 [124], JHCFUS [123]

Patients were not duplicated for the analysis of the addition of adjuvant chemotherapy.

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 11A: Classification of induction comparisons for subset analyzes

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
IGR-65[53]	< 1980	MonoCT without platin	Radiotherapy other*
RTOG 6801[54]	< 1980	MonoCT without platin	Radiotherapy other*
EORTC 24771[55]	< 1980	PolyCT without platin	Surgery and radiotherapy
Denver 77[56]	< 1980	PolyCT with platin	Other**
HNCPneo[38]	< 1980	PolyCT with platin	Surgery and radiotherapy
HNCPneo&adj[38]	< 1980	PolyCT with platin	Surgery and radiotherapy
EORTC 78-OCP[57]	< 1980	PolyCT without platin	Other**
MCW-1[58,59]	< 1980	PolyCT without platin	Other**
SWOG 8006[60]	1980-1993	PolyCT with platin	Surgery and radiotherapy
Pitié-81[44]	1980-1993	PolyCT with platin	Radiotherapy other*
Buenos Aires[34]	1980-1993	PolyCT with platin	Other**
Créteil-82[61]	1980-1993	PolyCT with platin	Other**
HNCGIC 02[62]	1980-1993	PolyCT with platin	Conventional radiotherapy
MCW-2[65,66]	1980-1993	PolyCT with platin	Other**
AC Camargo[39]	1980-1993	PolyCT with platin	Conventional radiotherapy
SECOG IIneo (unpublished)	1980-1993	PolyCT without platin	Radiotherapy other*
SECOG IIneofr (unpublished)	1980-1993	PolyCT without platin	Radiotherapy other*
SECOG IIneofnr (unpublished)	1980-1993	PolyCT without platin	Radiotherapy other*
EORTC 24844 (unpublished)	1980-1993	PolyCT with platin	Surgery and radiotherapy
SHNG-85[67]	1980-1993	PolyCT with platin	Conventional radiotherapy
Créteil-86[68,69]	1980-1993	PolyCT with platin	Other**
HNCGIC 03[63]	1980-1993	PolyCT with platin	Conventional radiotherapy
GSTTC-86[70,71]	1980-1993	PolyCT with platin	Conventional radiotherapy
GSTTC-86po[70,71]	1980-1993	PolyCT with platin	Surgery and radiotherapy
GETTECneo 1[25]	1980-1993	PolyCT with platin	Conventional radiotherapy
GETTECneo 2[25]	1980-1993	PolyCT with platin	Surgery and radiotherapy
AHNTG[72]	1980-1993	PolyCT with platin	Conventional radiotherapy
AHNTGsurg[72]	1980-1993	PolyCT with platin	Surgery and radiotherapy
Las Palmas[73]	1980-1993	PolyCT with platin	Conventional radiotherapy
Rennes-87[74]	1980-1993	PolyCT with platin	Other**
Parma[75]	1980-1993	PolyCT with platin	Other**
CFHNS[76,77]	1980-1993	PolyCT with platin	Other**
Songkhla[64]	1980-1993	PolyCT with platin	Surgery and radiotherapy
Cologne 88[78]	1980-1993	PolyCT with platin	Surgery and radiotherapy
HNAP 02[79]	1980-1993	PolyCT with platin	Other**
BNH 003 (unpublished)	1980-1993	PolyCT with platin	Surgery and radiotherapy
Lucknow 95[37]	1994-2000	MonoCT with platin	Conventional radiotherapy

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
TTCC 2002 PF -[2]	2001-2010	PolyCT with platin	Conventional radiotherapy
TTCC 2002 PF +[2]	2001-2010	PolyCT with platin	Conventional radiotherapy
TTCC 2002 TPF -[2]	2001-2010	PolyCT with platin	Conventional radiotherapy
TTCC 2002 TPF +[2]	2001-2010	PolyCT with platin	Conventional radiotherapy
GSTTC 2501[41,80]	2001-2010	PolyCT with platin	Conventional radiotherapy
DeCIDE[81]	2001-2010	PolyCT with platin	Radiotherapy other*
Budapest 2007[13]	2001-2010	PolyCT with platin	Conventional radiotherapy
Shanghai 2008 [82,83]	2001-2010	PolyCT with platin	Surgery and radiotherapy

* Alternating hypofractionated, radiotherapy …
** Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.

5-FU: 5-Fluorouracil, MonoCT: Monochemotherapy, PolyCT: Polychemotherapy

See Web-Table 1 for trials abbreviations.

Web-Table 11B: Classification of concomitant comparisons for subset analyzes

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
MDA-70[45]	< 1980	MonoCT without platin	Radiotherapy other*
WIA-0C5a[27]	< 1980	MonoCT without platin	Conventional radiotherapy
WIA-0C5b[27]	< 1980	MonoCT without platin	Conventional radiotherapy
Bergen[94]	< 1980	MonoCT without platin	Other**
EORTC73-OC[84]	< 1980	MonoCT without platin	Conventional radiotherapy
RT-BLM-73[95]	< 1980	MonoCT without platin	Conventional radiotherapy
WIA-OC5c[27]	< 1980	MonoCT without platin	Conventional radiotherapy
Turku[85]	< 1980	MonoCT without platin	Other**
UW-77[49]	< 1980	PolyCT without platin	Radiotherapy other*
NRH-78[86]	< 1980	MonoCT without platin	Other**
Barcelona[30]	< 1980	MonoCT without platin	Conventional radiotherapy
UW-79[50]	< 1980	PolyCT with platin	Radiotherapy other*
Manchester[87,88]	< 1980	MonoCT without platin	Radiotherapy other*
Yale-80npo[96]	1980-1993	MonoCT without platin	Conventional radiotherapy
Yale-80po[96]	1980-1993	MonoCT without platin	Surgery and radiotherapy
PMHCGS[97]	1980-1993	PolyCT without platin	Radiotherapy other*
ECOG 2382[89,90]	1980-1993	MonoCT with platin	Conventional radiotherapy
AC Camargo[39]	1980-1993	PolyCT with platin	Conventional radiotherapy
Toulouse[98]	1980-1993	MonoCT with platin	Surgery and radiotherapy
SECOG IIconc (unpublished)	1980-1993	PolyCT without platin	Conventional radiotherapy
SECOG IIconcfr (unpublished)	1980-1993	PolyCT without platin	Conventional radiotherapy
SECOG IIconcfnr (unpublished)	1980-1993	PolyCT without platin	Conventional radiotherapy

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
CH-7401[51]	1980-1993	PolyCT with platin	Other**
Torino 85[19]	1980-1993	MonoCT with platin	Conventional radiotherapy
Yale-86npo[99]	1980-1993	MonoCT without platin	Conventional radiotherapy
Yale-86po[99]	1980-1993	MonoCT without platin	Surgery and radiotherapy
Ontario[91]	1980-1993	MonoCT without platin	Conventional radiotherapy
Kragujevac1[35]	1980-1993	MonoCT with platin	Conventional radiotherapy
LOHNG-91[93]	1980-1993	PolyCT without platin	Conventional radiotherapy
Créteil 85[20]	1980-1993	PolyCT with platin	Conventional radiotherapy
INRC HN-8[100,101]	1980-1993	PolyCT with platin	Conventional radiotherapy
Bavaria-89[92]	1980-1993	PolyCT with platin	Radiotherapy other*
Lucknow 90[52]	1980-1993	PolyCT without platin	Conventional radiotherapy
RPC 3250[102]	1980-1993	PolyCT with platin	Conventional radiotherapy
Duke 90040[103]	1980-1993	PolyCT with platin	HF or Acc radiotherapy
Vienna[29]	1980-1993	MonoCT without platin	HF or Acc radiotherapy
UKHAN1npo1[42]	1980-1993	MonoCT without platin	Radiotherapy other*
UKHAN1npo1*[42]	1980-1993	MonoCT without platin	Radiotherapy other*
UKHAN1po1[42]	1980-1993	MonoCT without platin	Surgery and radiotherapy
UKHAN1npo2[42]	1980-1993	PolyCT without platin	Radiotherapy other*
UKHAN1npo2*[42]	1980-1993	PolyCT without platin	Radiotherapy other*
UKHAN1po2[42]	1980-1993	PolyCT without platin	Surgery and radiotherapy
Kragujevac 2[104]	1980-1993	MonoCT with platin	HF or Acc radiotherapy
IAR-92[46]	1980-1993	PolyCT with platin	HF or Acc radiotherapy
Torino 92[116]	1980-1993	MonoCT with platin	Conventional radiotherapy
Int 0126a[40]	1980-1993	MonoCT with platin	Conventional radiotherapy
Int 0126b[40]	1980-1993	PolyCT with platin	Conventional radiotherapy
RTOG 9111[31,32]	1980-1993	MonoCT with platin	Conventional radiotherapy
ORO-9301[28]	1980-1993	PolyCT with platin	Conventional radiotherapy
GORTEC 9401[105]	1994-2000	PolyCT with platin	Conventional radiotherapy
ARO 95-06[106]	1994-2000	PolyCT without platin	HF or Acc radiotherapy
EORTC 22931[107]	1994-2000	MonoCT with platin	Surgery and radiotherapy
SAKK 10-94 [108,109]	1994-2000	MonoCT with platin	HF or Acc radiotherapy
FCRT 94[119]	1994-2000	MonoCT with platin	Surgery and radiotherapy
FCRT 94*[119]	1994-2000	MonoCT with platin	Surgery and radiotherapy
UPCI 93-99[120]	1994-2000	MonoCT with platin	Surgery and radiotherapy
Cologne 95[43]	1994-2000	PolyCT with platin	HF or Acc radiotherapy
HeCOG 9405[36]	1994-2000	MonoCT with platin	Conventional radiotherapy
Lucknow 95[37]	1994-2000	MonoCT with platin	Conventional radiotherapy
RTOG 9501[110,111]	1994-2000	MonoCT with platin	Surgery and radiotherapy
EORTC 22954a (unpublished)	1994-2000	MonoCT with platin	Conventional radiotherapy

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
EORTC 22954b (unpublished)	1994-2000	MonoCT with platin	HF or Acc radiotherapy
EORTC-22962a (unpublished)	1994-2000	MonoCT with platin	Conventional radiotherapy
EORTC-22962b (unpublished)	1994-2000	MonoCT with platin	HF or Acc radiotherapy
IAEA-MMC[112]	1994-2000	MonoCT without platin	Conventional radiotherapy
GORTEC 9601[113]	1994-2000	PolyCT with platin	HF or Acc radiotherapy
NCI-V98-1416[114]	1994-2000	MonoCT without platin	Conventional radiotherapy
LOHNG-97[115]	1994-2000	PolyCT without platin	Surgery and radiotherapy
BiRCF[118]	1994-2000	PolyCT with platin	HF or Acc radiotherapy
AIIMS 2003[117]	2001-2010	MonoCT with platin	Conventional radiotherapy
TMH 1114[24]	1994-2000	MonoCT with platin	Conventional radiotherapy

* Alternating hypofractionated, radiotherapy. ** Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.

5-FU: 5-Fluorouracil, Acc: Accelerated, HF: Hyperfractionated, MonoCT: Mono chemotherapy, PolyCT: Polychemotherapy. See Web-Table 2 for trials abbreviations.

Web-Table 11C: Classification of adjuvant comparisons subsets analyzes

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
Pitié-74[33]	< 1980	PolyCT sans platine	Other**
HNCP*[38]	< 1980	MonoCT avec platine	Surgery and radiotherapy
DFCI[21]	< 1980	PolyCT avec platine	Other**
GETTECadj[121]	1980-1993	PolyCT avec platine	Surgery and radiotherapy
Int 0034[122]	1980-1993	PolyCT avec platine	Surgery and radiotherapy
JHCFUS[123]	1980-1993	MonoCT sans platine	Surgery
TMHR-4[124]	1980-1993	MonoCT sans platine	Surgery
KKD-86[125]	1980-1993	MonoCT sans platine	Surgery
HNU-87a[26]	1980-1993	MonoCT sans platine	Radiotherapy other*
HNU-87b[26]	1980-1993	MonoCT sans platine	Surgery
UKHAN1a1[42]	1980-1993	MonoCT sans platine	Radiotherapy other*
UKHAN1a1*[42]	1980-1993	MonoCT sans platine	Radiotherapy other*
UKHAN1a2[42]	1980-1993	PolyCT sans platine	Radiotherapy other*
UKHAN1a2*[42]	1980-1993	PolyCT sans platine	Radiotherapy other*

* Alternating hypofractionated, radiotherapy. ** Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.

MonoCT: Mono chemotherapy, PolyCT: Polychemotherapy

See Web-Table 3 for trials abbreviations.

Web-Table 12A: Variation of treatment effect according to the type of chemotherapy

	Hazard Ratio [95% CI]		
	Induction	**Concomitant**	**Adjuvant**
Overall survival			
PolyCT with platin salt	0.95 [0.89;1.01]	0.76 [0.69;0.84]	0.99 [0.84;1.17]
PolyCT without platin salt	0.98 [0.82;0.17]	0.82 [0.73;0.92]	1.13 [0.86;1.48]
MonoCT with platin salt	0.97 [0.73;1.29]	0.80 [0.74;0.86]	0.94 [0.70;1.26]
MonoCT without platin salt	0.99 [0.84;1.18]	0.90 [0.83;0.97]	1.04 [0.88;1.22]
Interaction	p=0.96	p=0.06*	p=0.80
Event-free survival			
PolyCT with platin salt	0.96 [0.90;1.02]	0.74 [0.67;0.82]	1.08 [0.85;1.38]
PolyCT without platin salt	0.97 [0.82;1.15]	0.85 [0.76;0.96]	0.98 [0.75;1.27]
MonoCT with platin salt	0.88 [0.67;1.17]	0.75 [0.69;0.81]	1.00 [0.76:1.33]
MonoCT without platin salt	0.96 [0.49;1.90]	0.86 [0.80;0.93]	0.94 [0.82;1.09]
Interaction	p=0.95	p=0.01*	p=0.81

* Analysis performed in two categories (with and without platin salt): p=0.02 for overall survival and p=0.001 for event-free survival
CI: Confidence interval, MonoCT: Monochemotherapy, PolyCT: Polychemotherapy

Web-Table 12B: Variation of treatment effect according to the start of accrual

	Hazard Ratio [95% IC]		
	Induction	**Concomitant**	**Adjuvant**
Overall survival			
< 1980	0.98 [0.88;1.10]	0.82 [0.74;0.91]	0.86 [0.67;1.09]
1980-1993	0.94 [0.87;1.02]	0.85 [0.79;0.90]	1.06 [0.95;1.18]
1994-2000	0.97 [0.73;1.29]	0.81 [0.75;0.87]	NA
2001-2010	0.98 [0.84;1.13]	0.63 [0.41;0.97]	NA
Interaction	p=0.92	p=0.48	p=0.12
Event-free survival			
< 1980	0.98 [0.85;1.12]	0.83 [0.75;0.93]	0.87 [0.69;1.09]
1980-1993	0.98 [0.91;1.06]	0.81 [0.76;0.86]	1.01 [0.90;1.14]
1994-2000	0.88 [0.67;1.17]	0.78 [0.72;0.84]	NA
2001-2010	0.89 [0.78;1.03]	0.66 [0.45;0.97]	NA
Interaction	p=0.66	p=0.53	p=0.23

CI: Confidence interval, NA: Not Applicable

Period of accrual was different for the trials included in the 3 timing trial subsets of the main question and for the secondary question: 37 trials between 1965 and 2012 for induction timing; 58 trials between 1970 and 2008 concomitant for timing with one trial ending accrual in 2008 and another in 2005, three in 2002 and the other before 2001; 11 trials between 1974 and 2000 for adjuvant timing with 10 trials between 1974 and 1990 and one between 1990 and 2000 [42] between 1980 and 2004 for the secondary question. For the induction trials, trials with TPF accrued between 2002 and 2012, those with PF between 1983 and 1993 (one TPF trial had also a PF arm, (TTCC 2002) [2] and the others between 1965 and 1999 (one trial accrued between 1995 and 1999 and the others before 1993).

Web-Table 12C: Variation of treatment effect according to loco-regional treatment

	Hazard Ratio [95% IC]		
	Induction	**Concomitant**	**Adjuvant**
Overall survival			
Surgery only	NA	NA	0.87 [0.67;1.14]
Conventional RT	0.96 [0.87;1.05]	0.83 [0.78;0.89]	NA
Hyperfractionated and/or accelerated RT	NA	0.78 [0.70;0.87]	NA
Other RT *	0.96 [0.84;1.10]	0.83 [0.74;0.93]	1.17 [0.99;1.38]
Surgery and RT	0.95 [0.85;1.07]	0.83 [0.73;0.93]	1.01 [0.87;1.17]
Other **	0.97 [0.85;1.11]	0.96 [0.77;1.21]	0.71 [0.47;1.10]
Interaction	p=0.99†	p=0.59‡	p=0.09§
Event-free survival			
Surgery only	NA	NA	0.77 [0.62;0.96]
Conventional RT	0.91 [0.83;1.00]	0.78 [0.73;0.83]	NA
Hyperfractionated and/or accelerated RT	NA	0.73 [0.66;0.81]	NA
Other RT *	0.83 [0.69;1.00]	0.88 [0.79;0.98]	1.10 [0.93;1.30]
Surgery and RT	1.02 [0.92;1.43]	0.83 [0.74;0.94]	1.11 [0.92;1.34]
Other **	1.04 [0.91;1.18]	0.97 [0.76;1.23]	0.64 [0.43;0.95]
Interaction	p=0.09†	p=0.06‡	p=0.005§

* Alternating radiotherapy, hypofractionated RT …
** Mainly trials with several types of loco-regional treatment impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.
† Afters exclusion of the « other » category: p=0.99 for overall survival and p=0.10 for event-free survival.
‡ Afters exclusion of the « other » category: p=0.80 for overall survival and p=0.09 for event-free survival.
§ Afters exclusion of the « other » category: p=0.16 for overall survival and p=0.02 for event-free survival.

CI: Confidence interval, NA: Not Applicable, RT: Radiotherapy

Web-Table 13A: Variation of treatment effect according to patients' subgroups for induction comparisons

see Figure 3 for performance status subgroups

		LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% IC]	Interaction	Heterogeneity of interaction
Overall survival						
Sex 24 comparisons 3830 patients	Male	1024 / 1628	1041 / 1613	0.91 [0.83;0.99]	p=0.58	p=0.77
	Female	142 / 297	147 / 292	0.98 [0.77;1.23]		
Age 20 comparisons 3493 patients	< 50	234 / 383	200 / 359	1.06 [0.88;1.28]	p=0.09	p=0.59
	[50;60[	374 / 655	437 / 683	0.81 [0.71;0.93]		
	[60;70[	374 / 580	356 / 543	0.93 [0.80;1.08]		
	≥70	99 / 138	115 / 152	1.06 [0.81;1.39]		
Tumour site 14 comparisons 2184 patients	Oral cavity	212 / 323	181 / 292	0.99 [0.81;1.21]	p=0.32	p=0.89
	Oropharynx	251 / 428	251 / 416	1.02 [0.85;1.21]		
	Hypopharynx	140 / 188	172 / 214	0.80 [0.64;1.01]		
	Larynx	91 / 164	84 / 159	1.09 [0.81;1.46]		
Stage* 21 comparisons 3084 patients	III	350 / 590	356 / 600	0.96 [0.83;1.11]	p=0.28	p=0.16
	IV-low	168 / 256	164 / 260	1.05 [0.84;1.30]		
	IV-high	493 / 700	496 / 678	0.87 [0.76;0.98]		
Event-free survival						
Sex 24 comparisons 3830 patients	Male	1125 / 1628	1122 / 1613	0.91 [0.84;0.99]	p=0.38	p=0.91
	Female	162 / 297	171 / 292	0.98 [0.79;1.21]		
Age 20 comparisons patients	< 50	261 / 383	223 / 359	1.08 [0.90;1.28]	p=0.12	p=0.79
	[50;60[	425 / 655	482 / 683	0.83 [0.72;0.94]		
	[60;70[	399 / 580	378 / 543	0.94 [0.82;1.09]		
	≥70	101 / 138	121 / 152	0.89 [0.68;1.56]		
Tumour site 14 comparisons 2184 patients	Oral cavity	229 / 323	204 / 292	0.94 [0.78;1.14]	p=0.38	p=0.67
	Oropharynx	272 / 428	280 / 416	0.98 [0.83;1.16]		
	Hypopharynx	152 / 188	178 / 214	0.83 [0.66;1.03]		
	Larynx	110 / 164	92 / 159	1.12 [0.85;1.48]		
Stage* 20 comparisons 3 168 patients	III	393 / 590	384 / 600	1.01 [0.88;1.16]	p=0.17	p=0.06
	IV-low	183 / 256	184 / 260	0.99 [0.81;1.22]		
	IV-high	522 / 700	529 / 678	0.85 [0.76;0.96]		

* Stage III: T3N0 or T1-3N1, stage IV-low: T0-3N2, stage IV-high: T4 or N3

CI: Confidence interval, CT: Chemotherapy, LRT: Loco-Regional Control

Web-Table 13B: Variation of treatment effect according to patients' subgroups for concomitant comparisons *see Figure 3 for age subgroups*

		LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% CI]	Interaction	Heterogeneity of interaction
Overall survival						
Sex 34 comparisons 6788 patients	Male	2042 / 2902	2107 / 2836	0.83 [0.78;0.89]	p=0.82	p=0.21
	Female	350 / 523	363 / 527	0.82 [0.71;0.95]		
Performance status 25 comparisons 5450 patients	PS0	926 / 1384	958 / 1365	0.83 [0.76;0.91]	p=0.52	p=0.21
	PS1	914 / 1200	897 / 1129	0.81 [0.73;0.88]		
	PS≥2	131 / 179	147 / 193	0.93 [0.74;1.19]		
Tumour site 24 comparisons 4650 patients	Oral cavity	359 / 537	366 / 531	0.82 [0.71;0.95]	p=0.85	p=0.93
	Oropharynx	697 / 990	665 / 909	0.82 [0.73;0.91]		
	Hypopharynx	293 / 376	299 / 380	0.88 [0.75;1.04]		
	Larynx	305 / 464	324 / 463	0.81 [0.69;0.95]		
Stage* 33 comparisons 6145 patients	III	526 / 829	564 / 827	0.86 [0.76;0.97]	p=0.50	p=0.0006
	IV-low	512 / 767	521 / 748	0.85 [0.75;0.96]		
	IV-high	1161 / 1523	1149 / 1451	0.80 [0.73;0.86]		
Smoking status 10 comparisons 2427 patients	Never	133 / 204	112 / 176	0.95 [0.74;1.22]	p=0.38	p=0.11
	Former / Current	844 / 1107	718 / 940	0.84 [0.76;0.93]		
Event-free survival						
Sex 32 comparisons 6624 patients	Male	2136 / 2835	2225 / 2753	0.79 [0.75;0.84]	p=0.73	p=0.13
	Female	382 / 516	404 / 520	0.77 [0.67;0.89]		
Performance status 24 comparisons 5342 patients	PS0	980 / 1368	1030 / 1341	0.77 [0.70;0.84]	p=0.41	p=0.86
	PS1	963 / 1174	943 / 1093	0.79 [0.72;0.86]		
	PS≥2	142 / 175	166 / 191	0.90 [0.72;1.13]		
Tumour site 22 comparisons 4509 patients	Oral cavity	413 / 521	430 / 518	0.78 [0.68;0.89]	p=0.45	p=0.25
	Oropharynx	712 / 963	675 / 877	0.80 [0.72;0.89]		
	Hypopharynx	292 / 361	307 / 361	0.90 [0.77;1.05]		
	Larynx	327 / 457	333 / 451	0.76 [0.65;0.89]		
Stage* 31 comparisons 5989 patients	III	552 / 783	602 / 783	0.76 [0.68;0.85]	p=0.65	p=0.001
	IV-low	529 / 733	545 / 716	0.82 [0.73;0.92]		
	IV-high	1193 / 1467	1193 / 1388	0.77 [0.71;0.84]		
Smoking status 10 comparisons 2427 patients	Never	168 / 204	148 / 176	0.84 [0.67;1.05]	p=0.69	p=0.006
	Former / Current	915 / 1107	796 / 940	0.80 [0.72;0.88]		

* Stage III: T3N0 or T1-3N1, stage IV-low: T0-3N2, stage IV-high: T4 or N3

For these analyzes, the following comparisons were pooled: EORTC 22962a and EORTC 22962b, EORTC 22954a and EORTC 22954b, Int 0126a and Int 0126b [40], UKHAN1npo1 and UKHAN1npo1* and UKHAN1npo2 and UKHANnpo2*, UKHAN1po1 and UKHAN1po2 [42].

CI: Confidence interval, CT: Chemotherapy, LRT: Loco-Regional Control

Web-Table 14: Cause of death by age groups for concomitant comparison

148 dead patients excluded as age was missing.

	< 50 years				[50-60[				[60-70[				≥ 70			
	LRT		LRT + CT		LRT		LRT + CT		LRT		LRT + CT		LRT		LRT + CT	
Cancer	448	*48.5%*	356	*42.0%*	625	*44.9%*	517	*38.9%*	563	*44.4%*	420	*33.8%*	152	*38.5%*	125	*31.1%*
Other	80	*8.7%*	92	*10.8%*	156	*11.2%*	189	*14.2%*	156	*12.3%*	216	*17.4%*	74	*18.7%*	89	*22.1%*
Unknown	395	*42.8%*	400	*47.2%*	610	*43.9%*	622	*46.8%*	548	*43.4%*	606	*48.8%*	169	*42.8%*	188	*46.8%*

Web-Table 15: Characteristics of patients (concomitant versus induction chemotherapies)

	Concomitant		Induction		Total	
	N	***%***	**N**	***%***	**N**	***%***
Sex						
Male	496	*81.9*	492	*80.9*	988	*81.4*
Female	110	*18.1*	116	*19.1*	226	*18.6*
Age (years)						
<50	119	*19.6*	113	*18.6*	232	*19.1*
50-59	205	*33.8*	197	*32.4*	402	*33.1*
60-69	208	*34.3*	203	*33.4*	411	*33.9*
≥70	74	*12.2*	95	*15.6*	169	*13.9*
Median [IQR]	59 [52;65]		59 [51;66]		59 [52;66]	
Performance status						
PS 0	163	*26.9*	150	*24.7*	313	*25.8*
PS 1	189	*31.2*	194	*31.9*	383	*31.5*
PS ≥2	17	*2.8*	22	*3.6*	39	*3.2*
Unknown*	237	*39.1*	242	*39.8*	479	*39.5*
Tumour site						
Oral cavity	105	*17.3*	111	*18.3*	216	*17.8*
Oropharynx	228	*37.6*	221	*36.4*	449	*37.0*
Larynx	93	*15.4*	103	*16.9*	196	*16.1*
Hypopharynx	96	*15.8*	87	*14.3*	183	*15.1*
Others	84	*13.9*	86	*14.1*	170	*14.0*
T (TNM)						
T0	6	*1*	2	*0.3*	8	*0.7*
T1	18	*3.0*	21	*3.5*	39	*3.2*
T2	76	*12.5*	58	*9.5*	134	*11.0*
T3	281	*46.4*	305	*50.2*	586	*48.3*
T4	224	*37.0*	221	*36.4*	445	*36.7*
Tx	1	*0.2*	1	*0.2*	2	*0.2*
N (TNM)						
N0	179	*29.5*	204	*33.6*	383	*31.5*
N1	156	*25.7*	147	*24.2*	303	*25.0*
N2	133	*22.0*	124	*20.4*	257	*21.2*
N3	138	*22.8*	133	*21.9*	271	*22.3*
Stage (TNM)						
Stage II	5	*0.8*	8	*1.3*	14	*1.2*
Stage III	209	*34.5*	221	*36.4*	429	*35.3*
Stage IV	392	*64.7*	379	*62.3*	771	*63.5*
Total	**606**	***100***	**608**	***100***	**1214**	***100***

* Information not collected in three comparisons (475 patients)

Web-Table 16: Characteristics of patients included in comparisons with or without surgery

	Without surgery (N=12949)		With surgery (N=5503)		p-value
	N	%	N	%	
Sex					p=0.0006
Male	10447	*80.7*	4663	*84.7*	
Female	2138	*16.5*	818	*14.9*	
Unknown*	364	*2.8*	22	*0.4*	
Age (years)					p < 0.0001
<50	2832	*21.9*	1303	*23.7*	
50-59	4424	*34.2*	2054	*37.3*	
60-69	4033	*31.2*	1550	*28.2*	
≥70	1279	*9.9*	423	*7.7*	
Unknown*	381	*2.9*	173	*3.1*	
Performance status					p < <0.0001
PS0	4497	*34.7*	2068	*37.6*	
PS1	5002	*38.6*	1130	*20.5*	
PS≥2	947	*7.3*	116	*2.1*	
Unknown*	2503	*19.3*	2189	*40.0*	
Tumour site					p < 0.0001
Oral cavity	2612	*20.2*	1903	*34.6*	
Oropharynx	5249	*40.5*	1439	*26.2*	
Larynx	2330	*18.0*	906	*16.5*	
Hypopharynx	1952	*15.1*	1017	*18.5*	
Other	674	*5.2*	219	*4.0*	
Unknown*	132	*1.1*	19	*0.4*	
T (TNM)					p < 0.0001
T0-1	523	*4.0*	367	*6.7*	
T2	2122	*16.4*	1339	*24.3*	
T3	4616	*35.7*	2282	*41.5*	
T4	5245	*40.5*	1227	*22.3*	
Tx*	37	*0.3*	0	-	
Tis*	0	-	2	*< 0.1*	
Unknown*	406	*3.1*	286	*5.2*	
N (TNM)					p < 0.0001
N0	3722	*28.7*	2042	*37.1*	
N1	2219	*17.1*	1284	*23.3*	
N2	3932	*30.4*	1310	*23.8*	
N3	2074	*16.0*	439	*8.0*	
N+*	638	*4.9*	154	*2.8*	
Nx (without detail)*	3	*< 0.1*	0	-	
Unknown*	361	*2.8*	274	*5.0*	
Stage (TNM)					p < 0.0001
Stage 0*	0	-	2	*< 0.1*	
Stage I-II	784	*6.1*	548	*10.0*	
Stage III	3138	*24.2*	2035	*37.0*	
Stage IV	8655	*66.8*	2620	*47.6*	
Unknown*	372	*2.9*	300	*5.5*	

* Excluded from the estimation of p-value

Web-Table 17: Effect of chemotherapy according to sex in comparisons with or without surgery

		LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% CI]	Interaction
Overall Survival 101 comparisons (18055 patients)†					
With surgery	Male	1417 / 2377	1373 / 2286	0.96 [0.89;1.03]	p=0.001
	Female	162 / 415	208 / 403	0.67 |0.54;0.82]	
Without surgery	Male	3940 / 5277	3992 / 5170	0.87 [0.83;0.91]	p=0.15
	Femme	728 / 1042	755 / 1096	0.94 [0.85;1.04]	
Interaction chemotherapy*sex*surgery : p=0.0004					
Event-free survival 96 comparisons (16691 patients)†					
With surgery	Male	1400 / 2169	1345 / 2080	0.97 [0.90;1.05]	p=0.0021
	Female	174 / 375	218 / 364	0.69 [0.57;0.85]	
Without surgery	Male	3919 / 4936	4012 / 4815	0.83 [0.79;0.87]	p=0.47
	Female	723 / 956	778 / 1007	0.86 [0.78;0.96]	
Interaction chemotherapy*sex*surgery : p=0.002					

† Exclusion of two comparisons with missing sex for all patients.

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 18: Description of trials identified in 2019

Trial (year of publication)	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized	Median follow-up [range] (years)
Yi J et al (2017) [a] [x]	2002-12	OC, OP, HP, L	III, IV	C (concomitant)	30 mg/m² weekly	RT +S	50-70 Gy/5-7 wks	222/240	4.9 [5.8 ; 6.25]
Huang PW et al (2018) [b] [y]	2006-11	OP, HP, L	III, IV	C U (po) LA (po)	50 mg/m²d_1, $wks_{1,3,5,7,9,11}$ 300 mg/m²$d_{1\text{-}14}$, $wks_{1,3,5,7,9,11}$ 60 mg/m²$d_{1\text{-}14}$, $wks_{1,3,5,7,9,11}$	RT	70-76/7-7.5 wks	151/151	4.5 [0.25 ; 6.25]
Sadighi S et al (2015) [c] [z]	2009-11	OC	III, IVa	Induction Do C F	70-80 mg/m², 60 mg/m², 750 mg/m² x 5,	S + RT	DM	24/24	1.3 [NA]

C: Cisplatin ; d: day ; Do: Docetaxel ; DM : data missing ; F: 5-Fluorouracil ; Gy: Gray ; HP: Hypophraynx ; L: Larynx ; LA: Leucovorin ; NA: Not available ; NP: Nasopharynx ; O : Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per os ; U=Tegafur-Uracil ; wks: weeks

[a] After 50 Gy, tumor evaluation was performed. Responders (>80% reduction of the primary tumor) received an overall dose of 70 Gy with modified neck dissection for N2/N3 patients, non-responders underwent resection of the primary and modified neck dissection. For OS, the HR was 0.74 [0.50-1.10; p0.13].

[b] 151 out of the 200 planned patients were included. “The study was suspended because of slow accrual and poor end points in the ICT/CCRT arm during interim analysis. With insufficient statistical power, the OS in the ICT/CCRT arm was not poorer than that in the CCRT arm.” “in patients with advanced PLSCC. However, patients treated with ICT/CCRT had poorer PFS and LRC. The higher prevalence of hypopharynx cancer (57.1% vs 40.5%, p ¼ 0.09) and N2 or N3 disease (85.7% vs. 74.4%, p ¼ 0.02) in the ICT/CCRT arm may account for the poorer PFS and LRC.” The same chemotherapy regimen was given in both arms concurrently with radiotherapy. Median follow-up time was only for surviving patients. No value of hazard ratio for overall or progression-free survival was reported.

[c] After two cycles of chemotherapy, tumor response was evaluated with a third cycle in case of objective response. No value of hazard ratio for overall or progression-free survival was reported.

References:

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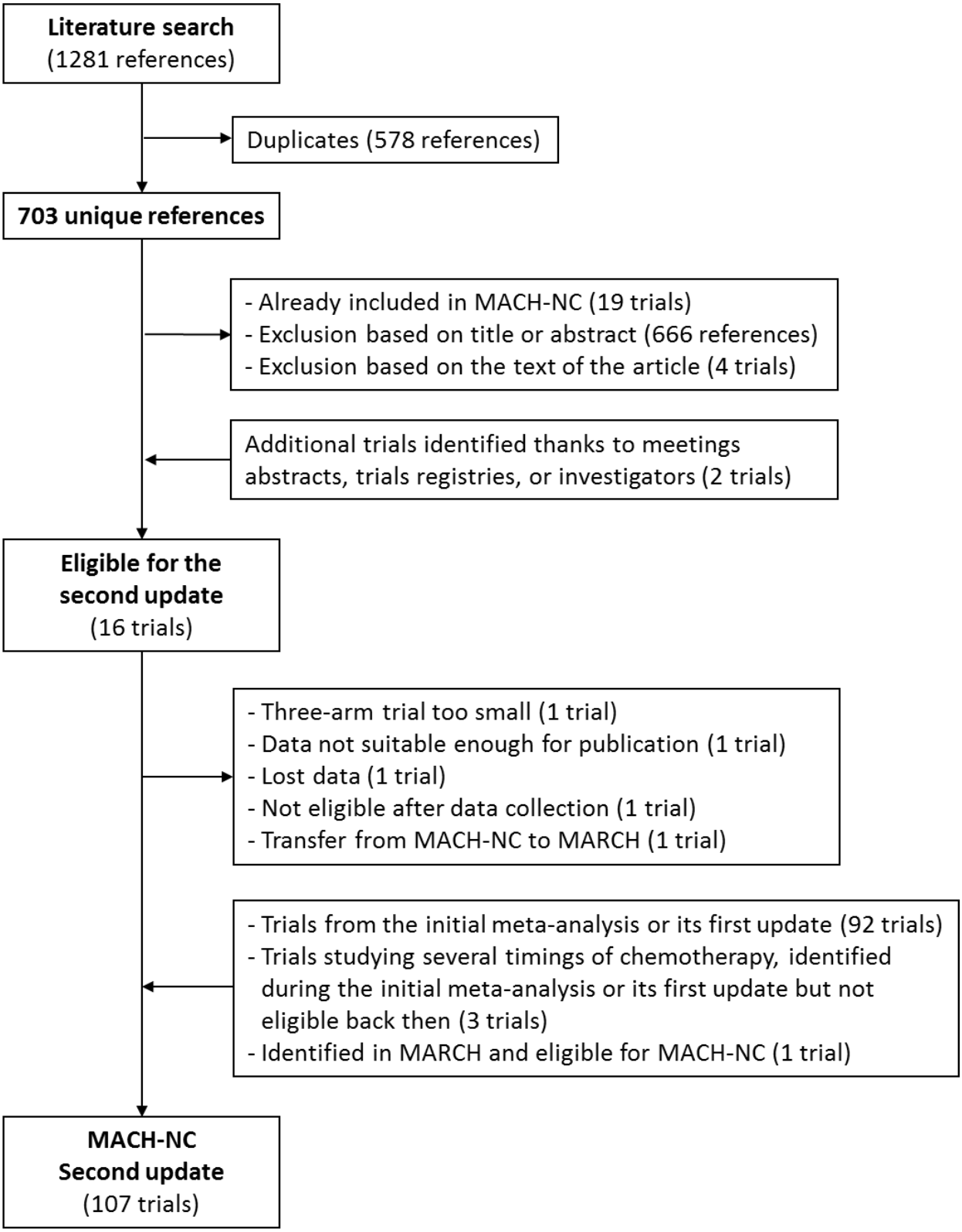
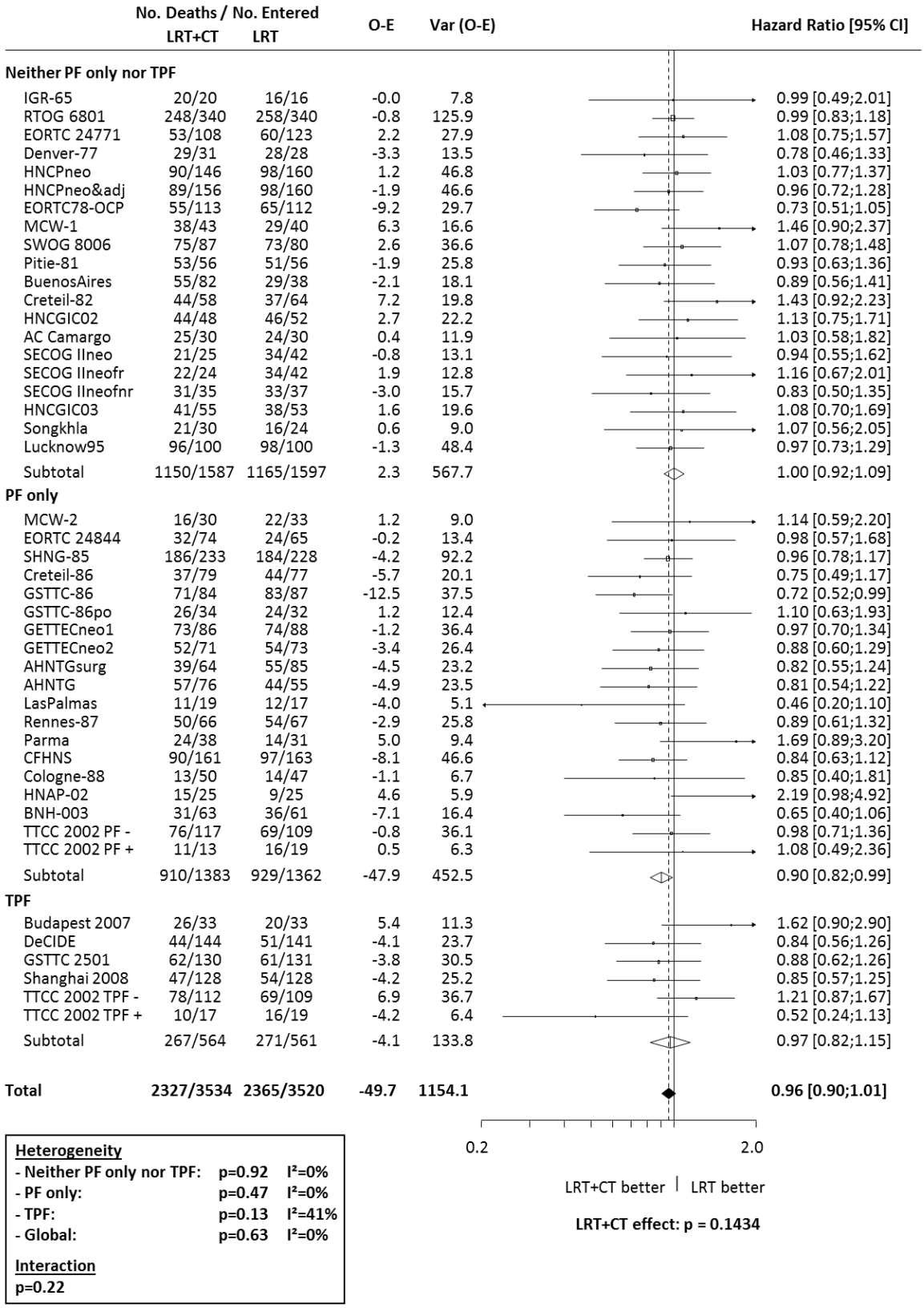
Web-Figure 1: Flowchart



MACH-NC: Meta-Analysis of Chemotherapy in Head and Neck Cancer, MARCH: Meta-Analysis of Radiotherapy in Head and Neck cancer

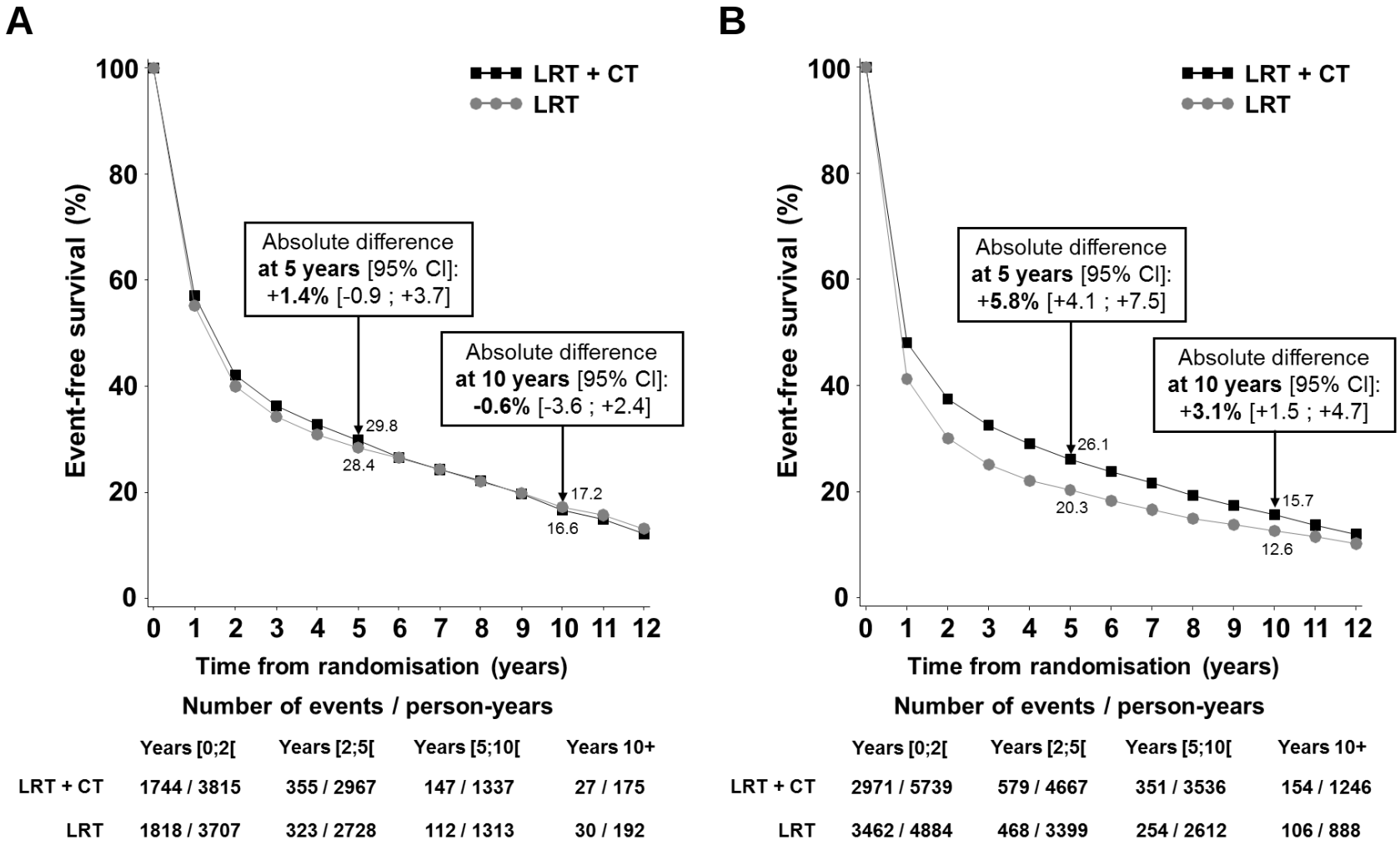
Web-Figure 2: Overall survival - Loco-regional treatment plus induction chemotherapy versus loco-regional treatment alone. *See Web-Table1 for trials abbreviations*



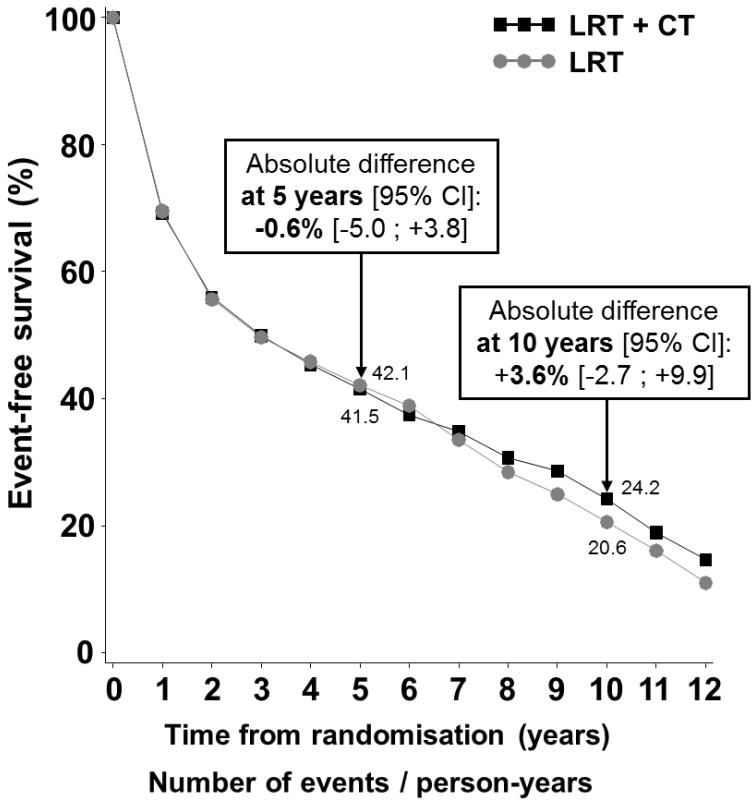
CI: Confidence Interval, CT: Chemotherapy, E: Expected, LRT: Loco-Regional Treatment, O: Observed, PF: 5-Fluorouracil + platin salt, TPF: 5-Fluorouracil + platin salt + taxane

Web-Figure 3: Event-free survival - Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing

A: Induction chemotherapy, B: Concomitant chemotherapy, C: Adjuvant chemotherapy.



C



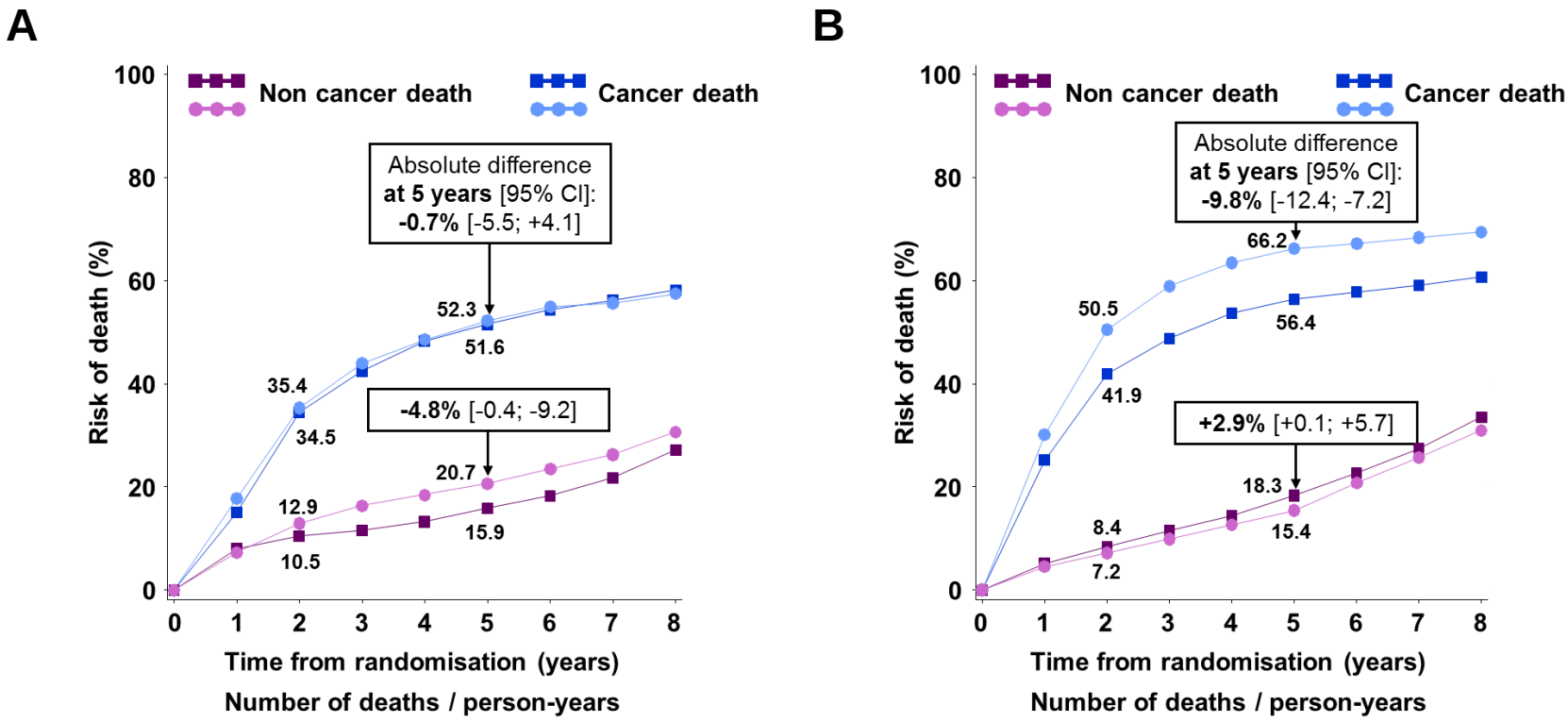
Number of events / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
LRT + CT	497 / 1659	123 / 1226	50 / 512	27 / 109
LRT	543 / 1752	131 / 1331	69 / 532	21 / 58

CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Figure 4: Cancer and non-cancer mortality - Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing

A: Induction chemotherapy, B: Concomitant chemotherapy.



Number of deaths / person-years

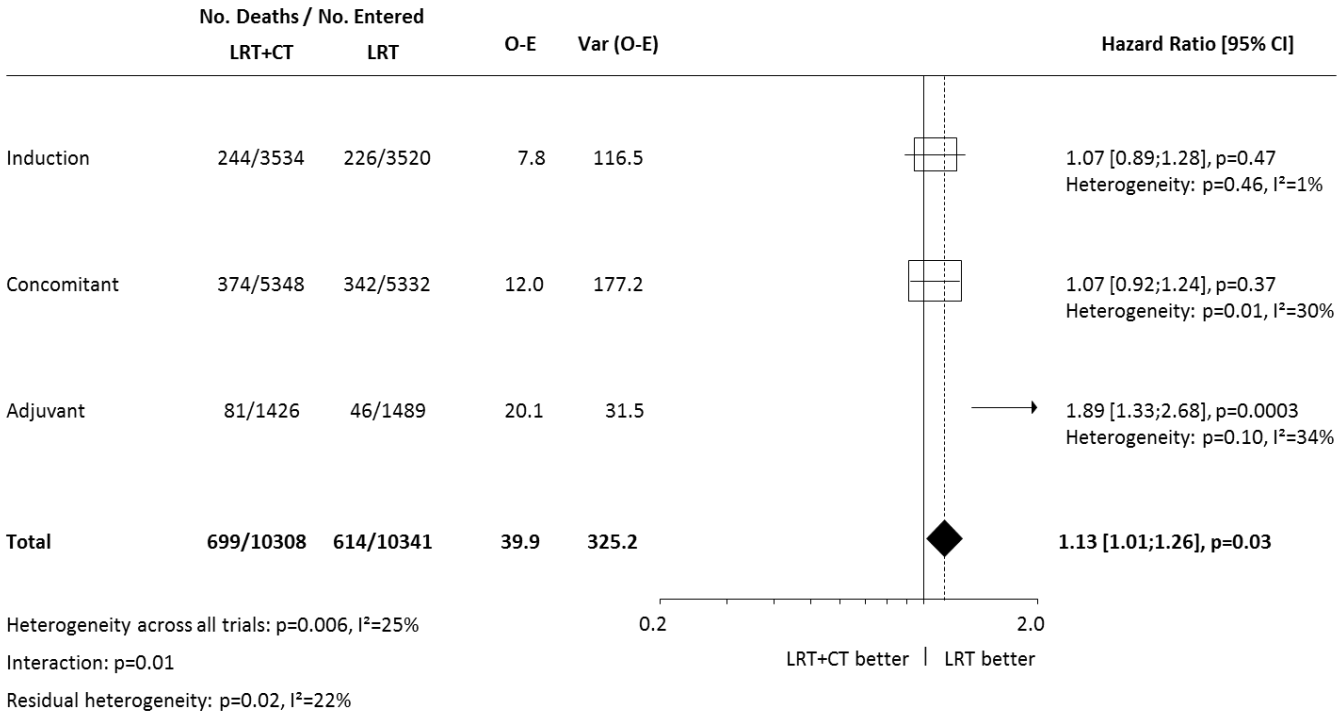
	Years [0-2[	Years [2-5[	Years 5+
LRT + CT	92 / 1537	24 / 1204	33 / 639
LRT	105 / 1479	35 / 1086	31 / 614
LRT + CT	324	139	37
LRT	324	128	27

Number of deaths / person-years

	Years [0-2[	Years [2-5[	Years 5+
LRT + CT	195 / 4358	123 / 3393	226 / 3041
LRT	167 / 4131	81 / 2637	163 / 2314
LRT + CT	1234	373	123
LRT	1503	387	110

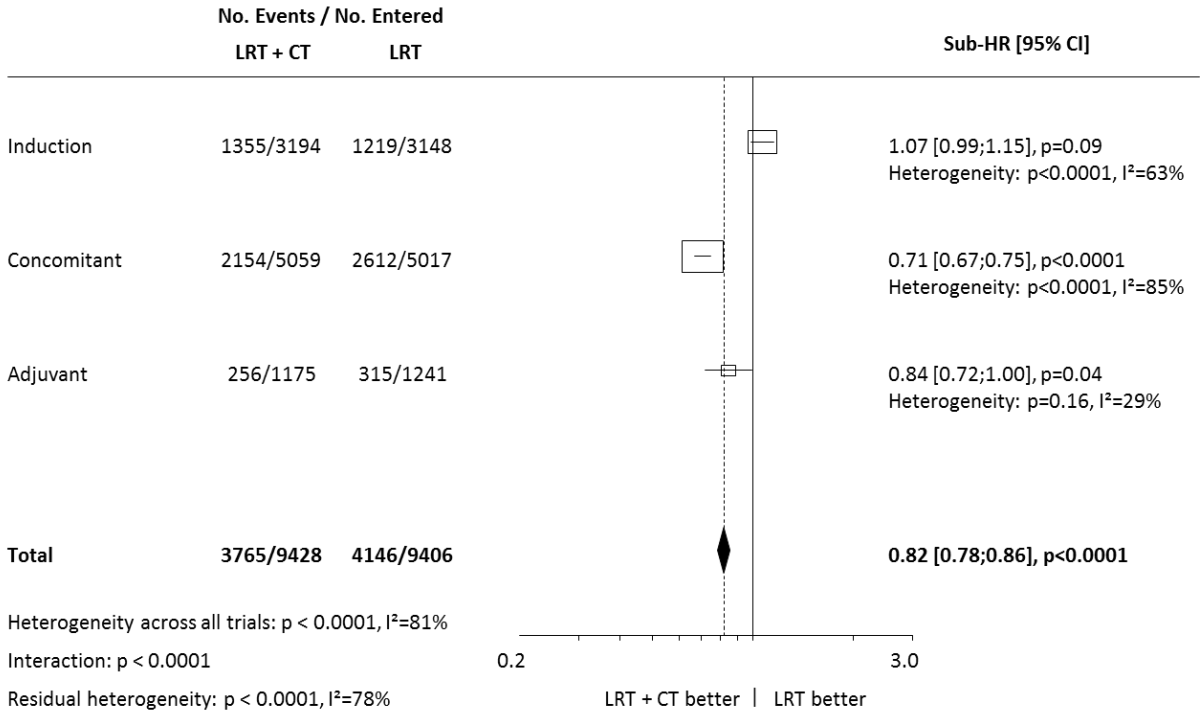
CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Figure 5: 120-day mortality - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone



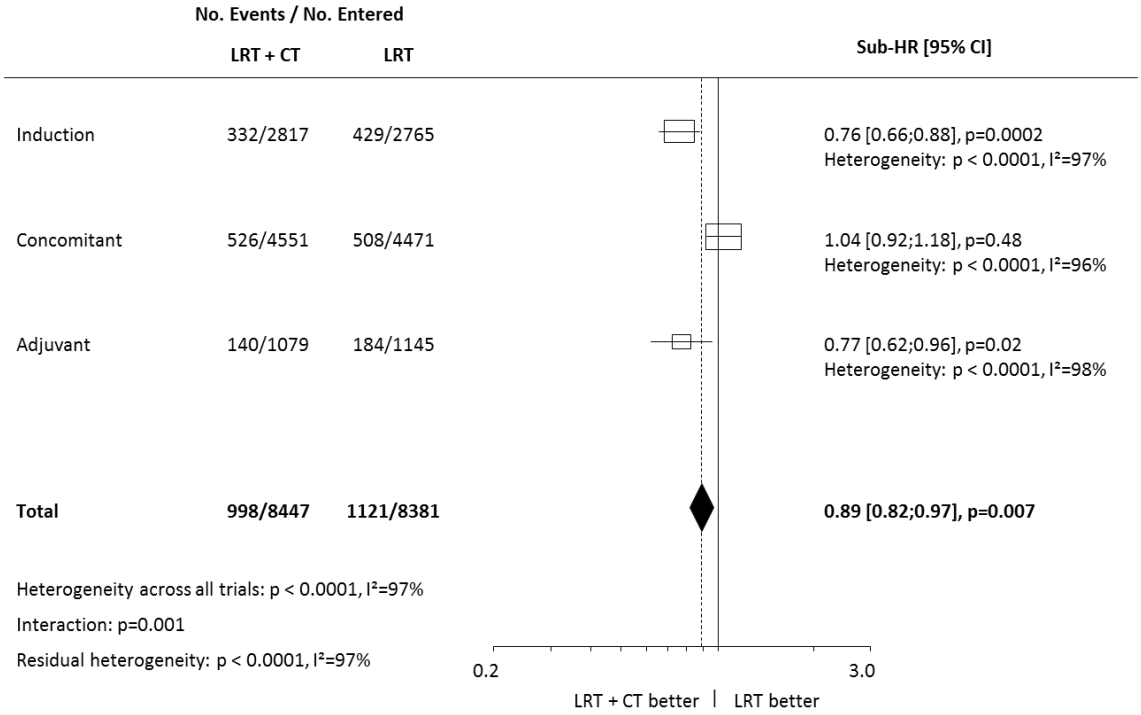
CI: Confidence Interval, CT: Chemotherapy, HR: Hazard Ratio, LRT: Loco-Regional Treatment, O-E: Observed minus Expected

Web-Figure 6: Loco-regional failure - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone



CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment, sub-HR: Sub-distribution Hazard Ratio

Web-Figure 7: Distant failure - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone

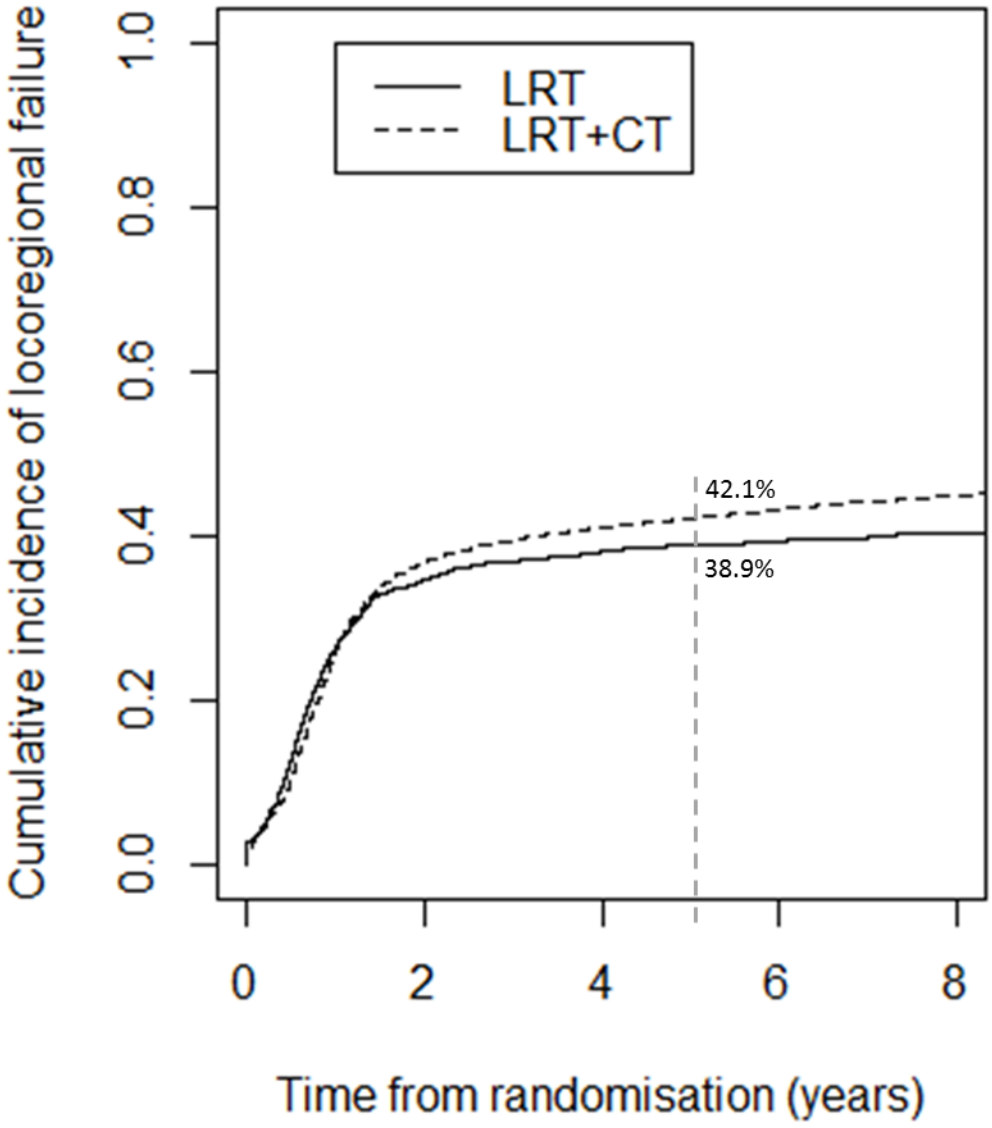


CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment, sub-HR: Sub-distribution Hazard Ratio

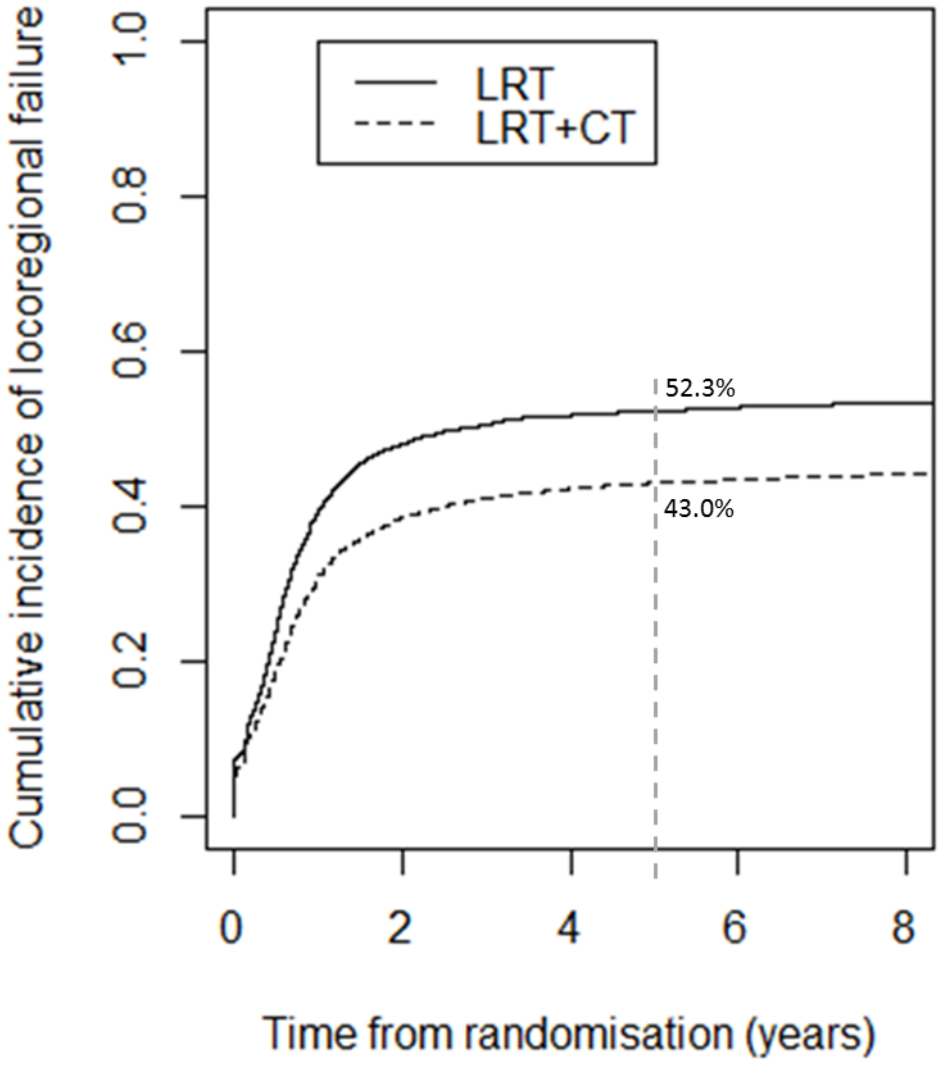
Similar results were observed after excluding the comparisons with a rate of distant failure inferior to 5% (data not shown)

Web-Figure 8: cumulative incidence of locoregional failure (LRF)

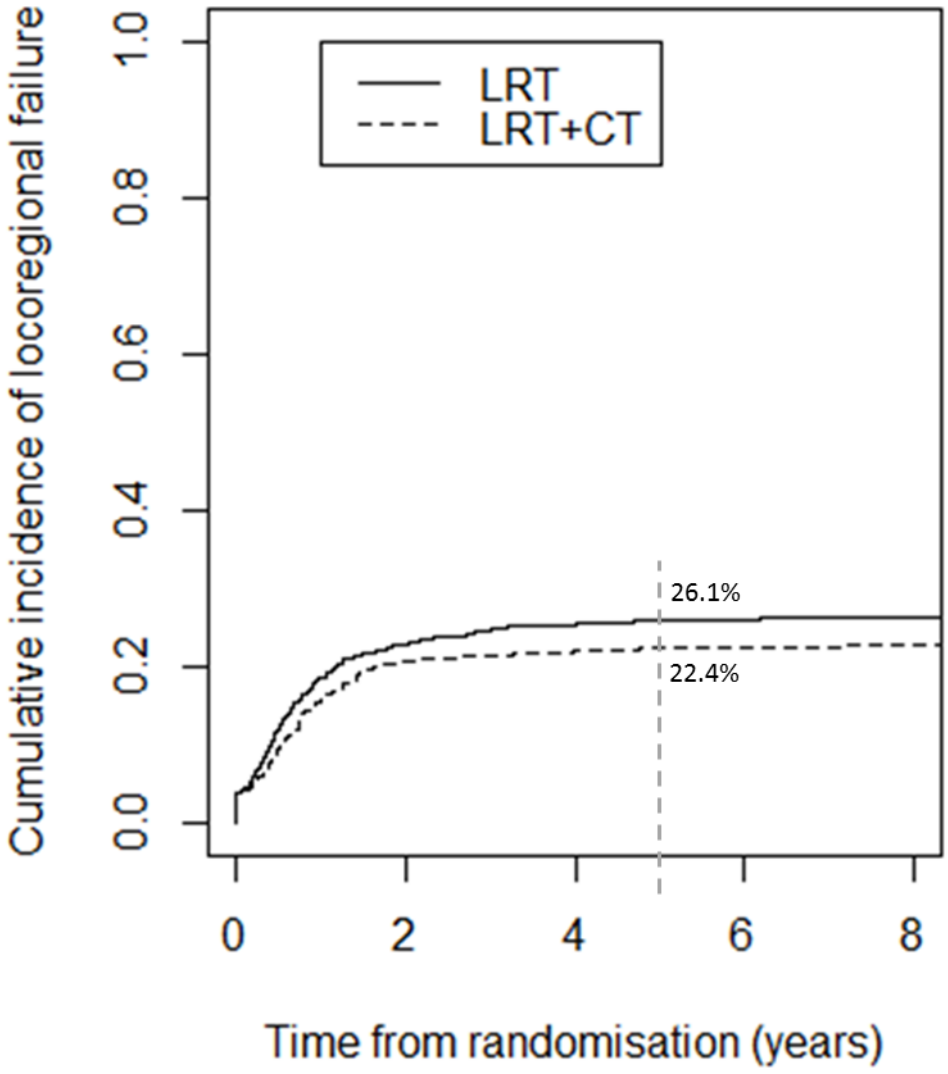
*Web-Figure **8-A**: LRF - Cumulative incidence in induction comparisons*



*Web-Figure **8-B**: LRF - Cumulative incidence in concomitant comparisons*

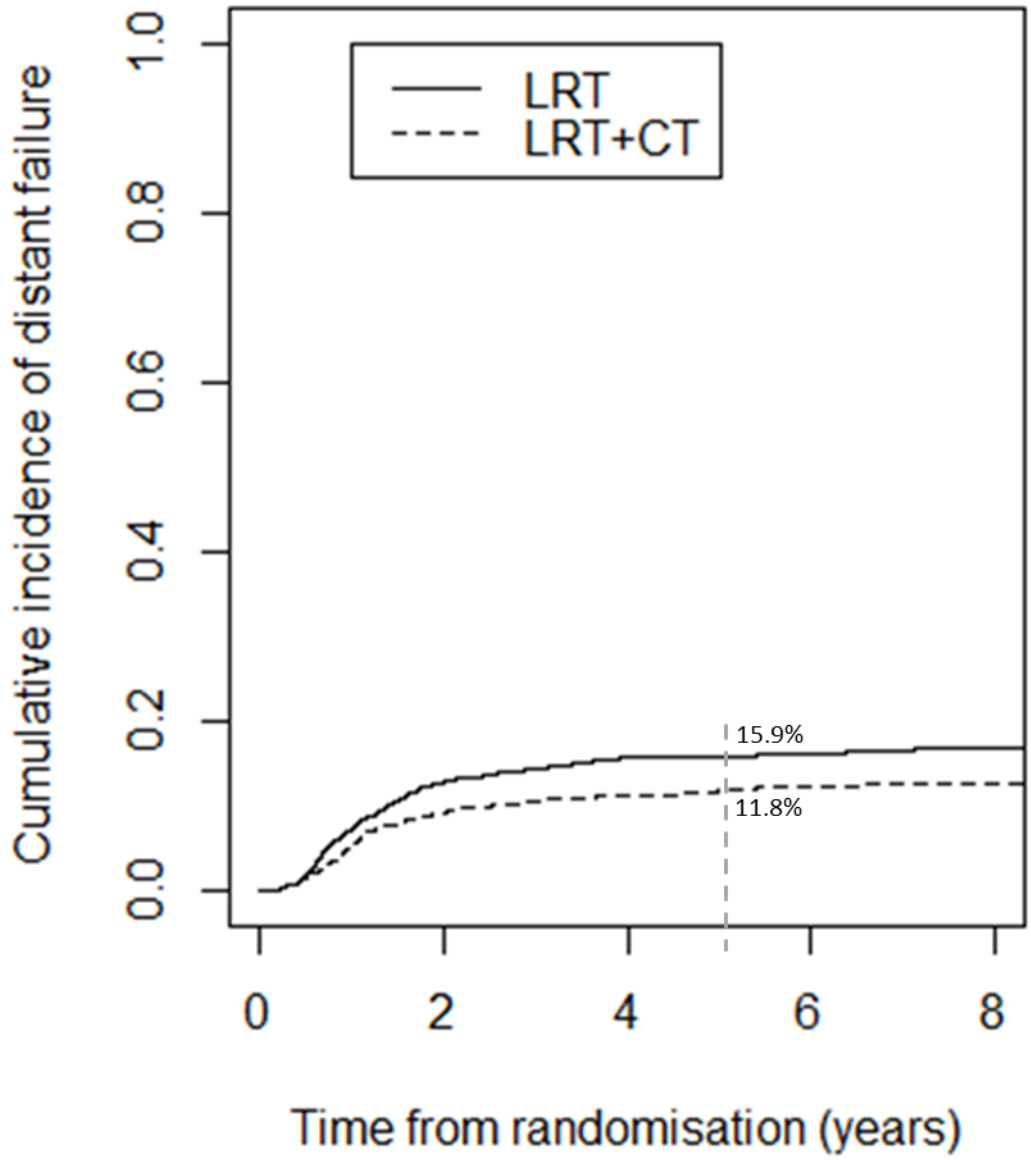


Web-Figure **8-C**: LRF - Cumulative incidence in adjuvant comparisons

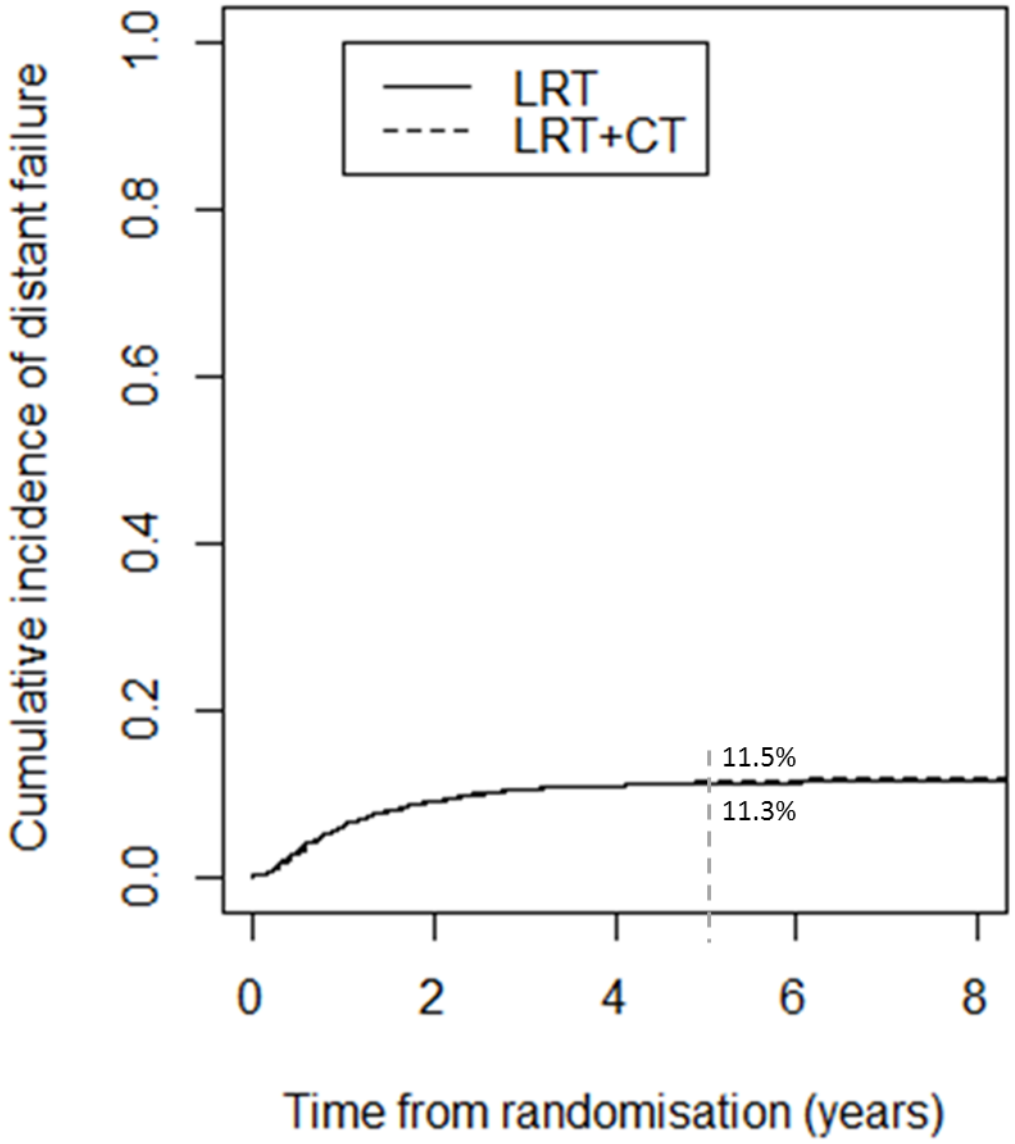


Web-Figure 9: cumulative incidence of distant failure (DF)

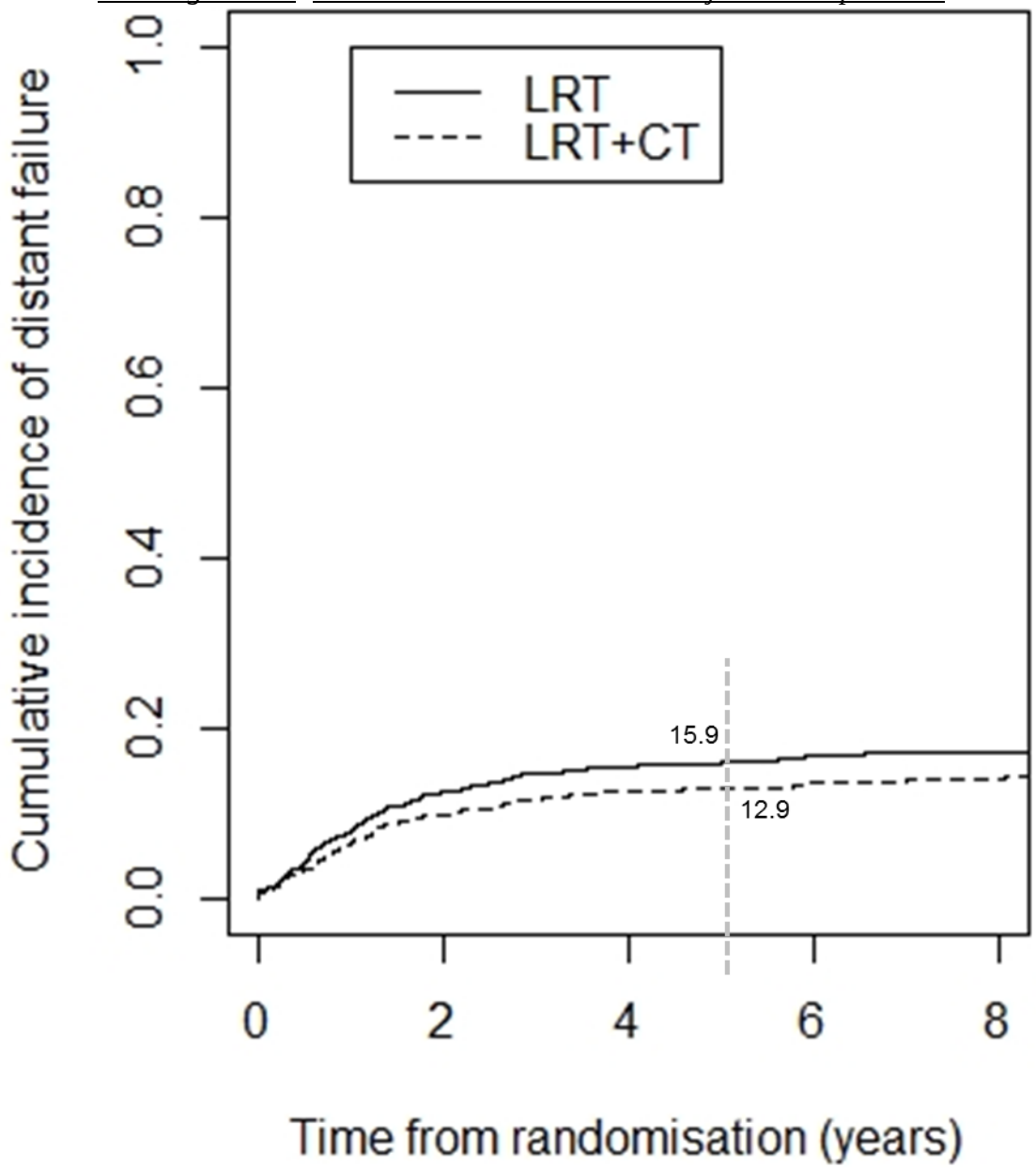
*Web-Figure **9-A**: DF - Cumulative incidence in induction comparisons*



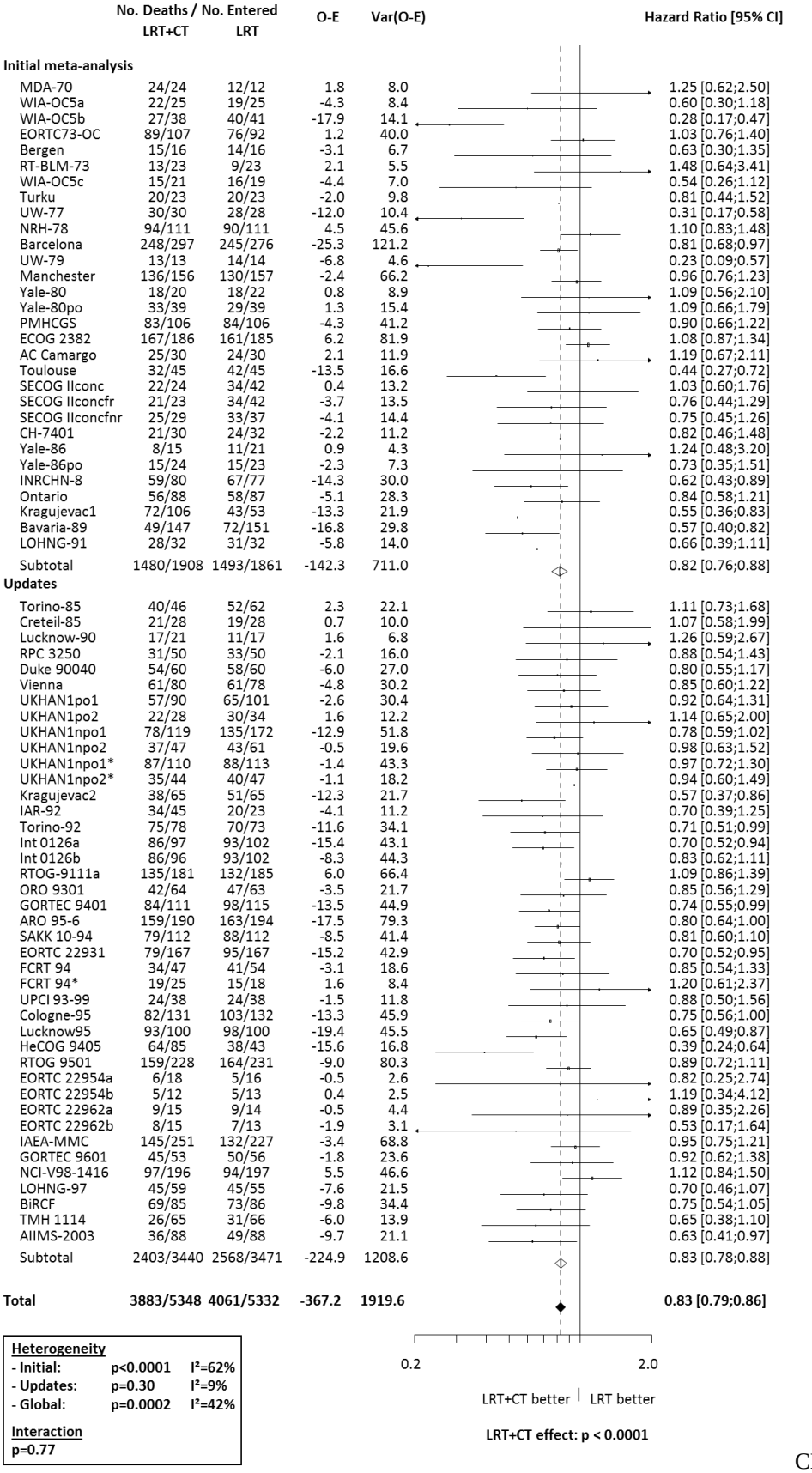
*Web-Figure **9-B**: DF - Cumulative incidence in concomitant comparisons*



*Web-Figure **9-C**: DF - Cumulative incidence in adjuvant comparisons*



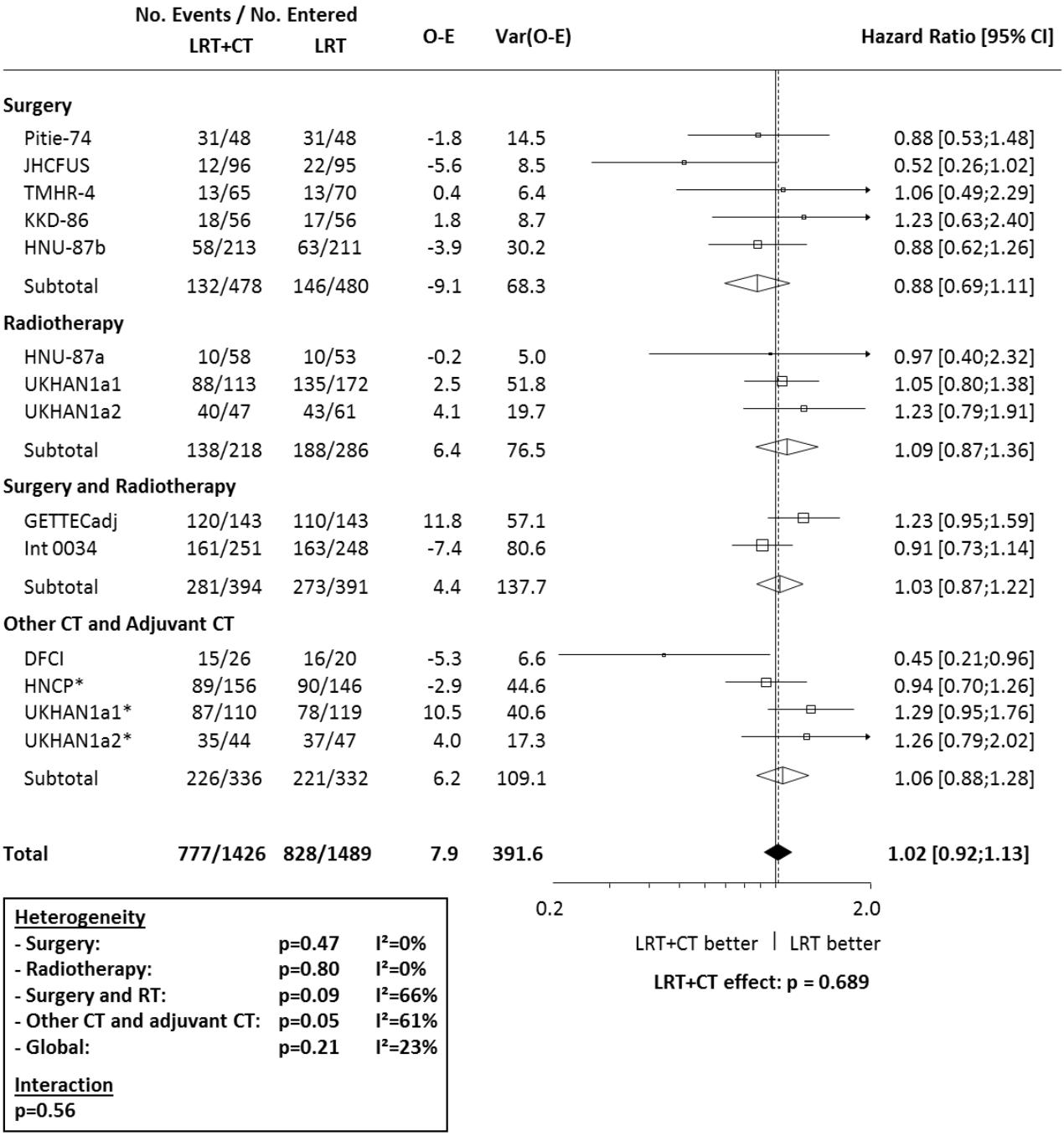
Web-Figure 10: Overall survival - Loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone. *See Web-Table 2 for trials abbreviations*



CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Figure 11: Overall survival - Loco-regional treatment plus adjuvant chemotherapy versus loco-regional treatment alone

See Web-Table 3 for trials abbreviations



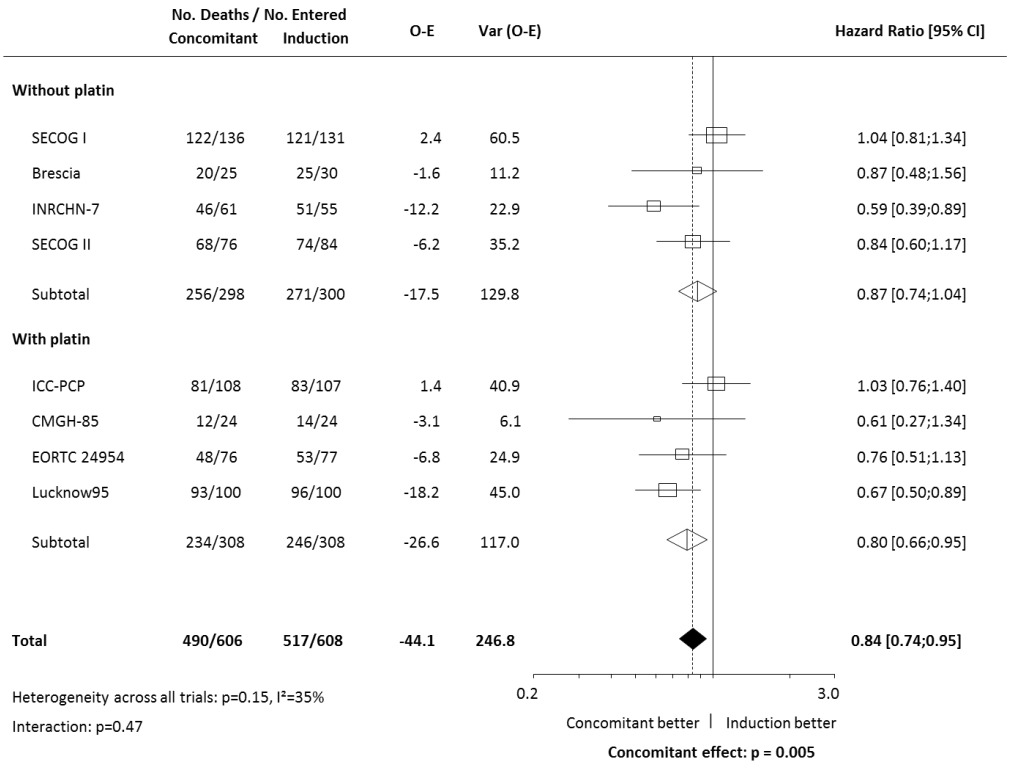
CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Note: trials on chemotherapy concomitant to postoperative radiotherapy were included in the concomitant timing.

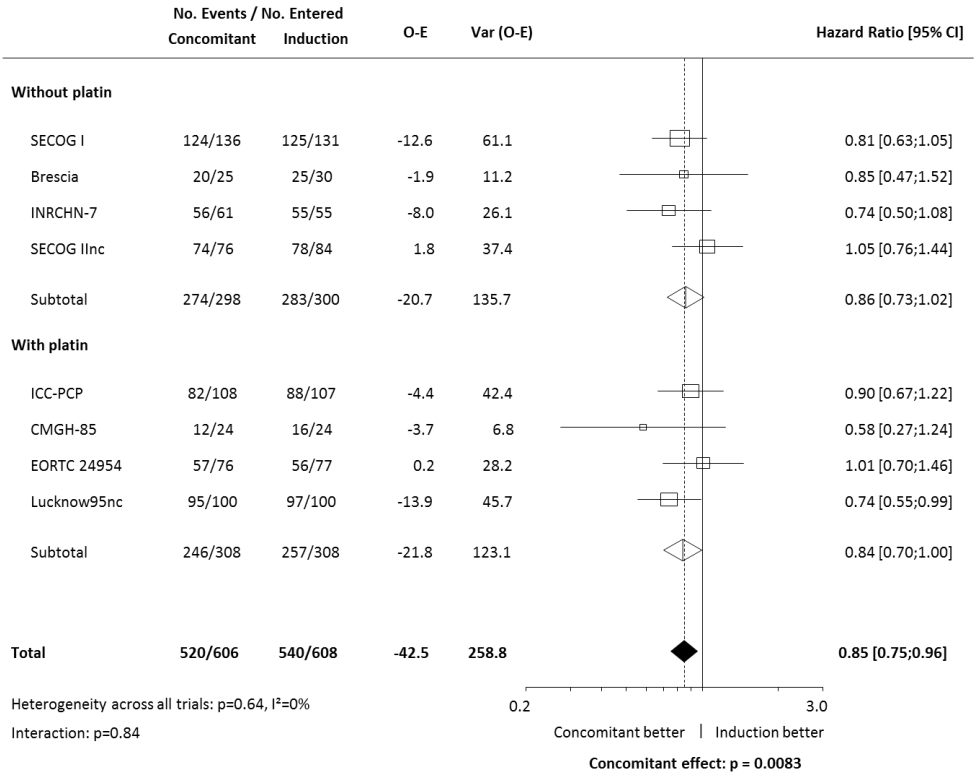
Web-Figure 12: Efficacy of concomitant versus induction chemotherapy.

A: Overall survival, B: Event-free survival. *See Web-Table-4 for trials abbreviations.*

A



B

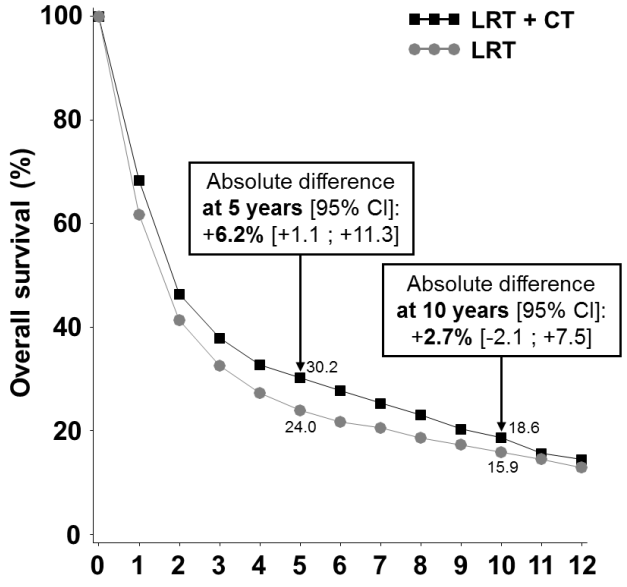


CI: Confidence Interval, CT: Chemotherapy, HR: Hazard Ratio, LRT: Loco-Regional Treatment, O-E: Observed minus Expected.

Web-Figure 13: Survival curves of concomitant versus induction chemotherapy

A: Overall survival, B: Event-free survival

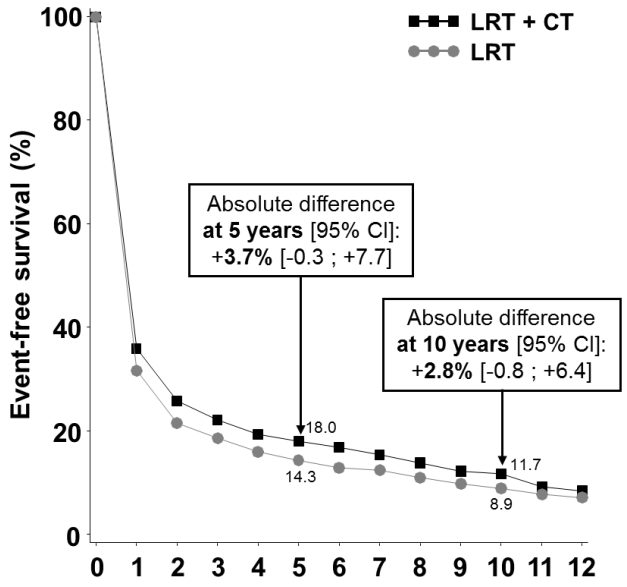
A



Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
LRT + CT	322 / 849	95 / 623	50 / 510	23 / 232
LRT	358 / 786	102 / 539	34 / 432	23 / 204

B



Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
LRT + CT	406 / 575	58 / 457	35 / 382	21 / 189
LRT	450 / 491	51 / 375	27 / 305	12 / 110

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

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